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ATROPINE, STRESS AND HUMAN PERFORMANCE

FINAL REPORT

Harold L. Williams
John Carney
Frank A. Holloway

August, 1987

Supported by
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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The University of Oklahoma Health Sciences Center
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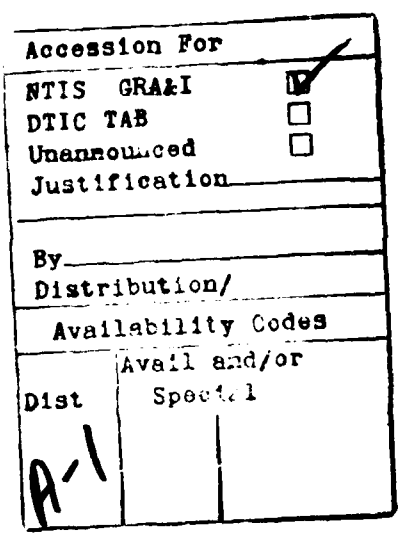

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With both atropine (2.0 mg) and sleep deprivation, subjects reported feeling less alert and more sleepy. The multiple sleep latency test confirmed these self-reports of reduced alertness. Atropine combined with sleep deprivation produces hyperadditive interaction effects on daytime sleepiness. Exercise effects on self-reports were inconsistent, reversing the atropine effects in Year 1 and potentiating them in Year 3.

In general, these data suggest that 2.0 mg of atropine administered after a sleepless night could lead to catastrophic performance failures in the field, particularly on tasks that demand rapid speed analysis of visual or auditory information.

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SUMMARY

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In general, these data suggest that 2.0 mg of atropine administered after a sleepless night could lead to an increase in performance failures in the field, particularly on tasks that demand vigilance ans rapid analysis of visual or auditory information.

FOREWORD

For the protection of human subjects, the investigators have adhered to policies of applicable Federal Law 45CFR46.

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1. Statement of the Problem

The overall goals of this research program were to investigate dose-related effects of atropine, alone and combined with two stress-related variables--pre-dose moderate exercise and/or a night of sleep deprivation--on cognitive performance, selected autonomic variables, self-reports and daytime sleepiness in healthy young men. The specific aims of the first year of work were to develop sensitive laboratory tasks and to conduct two investigations: (1) to examine the effects over about 4 hours of each of three intramuscular (i.m.) doses of atropine sulfate (0.5, 1.0 and 2.0 mg) on the cognitive tasks and autonomic variables; (2) to examine the effects of pre-dose physical exercise on the sensitivity of the cognitive and autonomic measures to the same three doses of atropine. The main goal of the second year of research was to investigate the independent and combined effects of a single 2.0 mg dose of atropine and a night of sleep deprivation on selected cognitive tasks and physiological variables. During the third year, the effects of three experimental variables, atropine, exercise and sleep deprivation, were investigated alone and in combination.

Selection of cognitive tasks and physiological measures for the second and third years was based on three considerations: (1) their apparent validity for certain information-processing requirements likely to be encountered in contemporary military jobs; (2) estimates of their probable sensitivity to anticholinergic compounds, sleep deprivation and exercise; and (3) the first year's research experience. The task modifications made in the second and third years permitted more refined analyses of the selective effects of atropine, sleep deprivation and exercise on input (perceptual) and output (response-related) components of information processing.

The dose-related effects of atropine on most of the autonomic variables selected for this research are rather well documented (1, 2, 3, 4), but we found no studies of these effects in combination with sleep deprivation or pre-dose exercise, nor are there any investigations of the independent or combined effects of these treatments on daytime sleepiness (sleep tendency) as assessed by the multiple sleep-latency test (5). The latter test was entered into the research protocol in year 2.

2. Rationale

The research literature indicates that relatively small doses of atropine may impair cognitive functions that are essential components of a number of military jobs in the field (4, 6). One night of sleep deprivation also causes impairment on tasks that have military relevance (7, 8, 9), and there are indications in recent research that the dose effects of atropine might interact hyperadditively with those of sleep deprivation to cause considerable performance impairment (9, 10, 11, 12).

The selection of pre-dose exercise as a second stress-related

variable was based on the investigations of Carney et al. (13) in rodents. They found that when rats performed moderate pre-dose treadmill exercise, atropine dose effects on schedule-controlled operant behavior were potentiated. From both scientific and military perspectives, it is important to ascertain whether the three treatments--atropine, sleep deprivation and pre-dose exercise--have additive or hyperadditive effects on human performance.

3. Background and Literature Review

a. Dose effects of atropine on information processing, selected autonomic variables, self-reports and sleep latency

a.1 Some pharmacological considerations

Atropine is a belladonna alkaloid which inhibits parasympathetic nervous system functions through its antagonism of acetylcholine. As such, it has well-known applications as a medication for gastrointestinal disorders, ophthalmologic examinations, and respiratory and cardiac dysfunctions and as an antidote for organophosphate poisoning by pesticides and nerve gases (14). Atropine is prototypical of a class of cholinergic antagonists characterized as muscarinic cholinergic blocking agents (14). The basic differences between atropine and such congeners as scopolamine are relative potency and site of action. For example, scopolamine exhibits a central nervous system (CNS) potency about 30 times that of atropine, but with little peripheral autonomic activity (15). Nevertheless, the effects of atropine and scopolamine on CNS functions are qualitatively similar so that assessments of their centrally mediated behavioral effects appear to be conceptually interchangeable (16). This is important for discussions to follow because several apposite studies of cholinergic drug effects on information processing employed scopolamine rather than atropine (10, 11, 12, 17, 18).

a.2 Information processing

Most studies of the effects of cholinergic drugs on cognitive and psychomotor functions have been task focused and empirical (4). Typically, such research employs a battery of performance tasks, each of which challenges a variety of skills. Although the test score profiles may differ systematically for different experimental variables (e.g., different drugs), precise conclusions about which cognitive functions are selectively affected by a given treatment are seldom possible. The tasks used in such studies often lack a theoretical rationale, and the skill components represented in each task are usually too complexly organized for precise functional analysis. Headley (4), reviewing the visual, physiological, subjective and behavioral effects of atropine, reported dose-related decrements in visual perception, divided attention, time perception, judgment, reasoning, learning, memory and reaction time. Absent some sort of theoretical formulation, it is not possible to guess whether these multiple

deficits are due to impairment of one or of many basic cognitive functions.

For the first year of this research program, the experimental protocols were also primarily task oriented and empirical. However, the findings from that year, considered with some relatively recent results and theory from other investigators, led to hypotheses about specific functional impairments likely to be observed with a moderate dose of atropine. The laboratory tasks developed for the second and third years of research were designed to test these hypotheses.

In his 1977 review, Warburton (10) concluded that the central ascending cholinergic reticular pathways selectively mediate the recognition and selection of environmental stimuli and not the selection, organization and execution of responses. Evidence for this hypothesis came first from animal studies, in which cholinergic agonists such as physostigmine improved stimulus detection performance (11), whereas cholinolytics such as scopolamine disrupted stimulus detection performance (12). Statistical analyses of data collected by Brown and Warburton (12), based on signal detection theory (19), showed that these changes in stimulus detection performance resulted from drug-induced alterations in perceptual sensitivity (d') rather than alterations in criteria for responding or willingness to respond (β). Warburton and his colleagues concluded that central muscarinic blockade disrupts signal detection performance by causing specific impairment of perceptual sensitivity (12). Later, Wesnes and Warburton (18) showed that two compounds, scopolamine and nicotine, having opposite effects on central cholinergic functions, caused opposite effects on visual signal detection in a high-speed information-processing task. Callaway (20) employed a serial-stage information-processing theoretical model of choice reaction time along with Sternberg's (21) additive factor method to investigate the effects of several psychotropic chemicals on human performance. Using event-related brain potentials elicited by stimuli within information-processing tasks, Callaway's results were similar to those of Warburton and his colleagues in that scopolamine impaired input functions associated with stimulus identification, but not output functions such as response selection and response execution.

More recently, Dunne and Hartley (22) concluded that impairments of retention by scopolamine were due to its effects on selective attention rather than on memory functions per se. They suggested that the central cholinergic system may be involved in the control of effortful information-processing functions, and that cholinergic blockade reduces the degree of control that the organism has over such effortful functions as the selection of task-relevant information. Collectively these effects suggest that the disruptions of information processing caused by the muscarinic cholinergic antagonists are due either to direct effects on such computational operations as stimulus evaluation, or to their effects on supporting operations such as the supply

and distribution of attention-serving energetical resources. In either case, the dichotomy between stimulus processing and response processing suggested by these investigations matches the functional distinction between cholinergic and aminergic neurochemical systems noted by others. For example, Vanderwolf and Robinson (23) suggest that there are two different kinds of input from the reticular activating system to the hippocampus and cerebral cortex. One input system appears to be cholinergic and may have important roles in selective attention and stimulus identification. The second input is probably aminergic and appears to be related to motor functioning.

a.3 Autonomic functions

The primary peripheral functions of the muscarinic cholinergic system are the mediation of exocrine gland activity and the activity of the parasympathetic nervous system (PNS). Reduction in PNS activity by competitive binding of atropine to the muscarinic receptors results in dose-related depression of salivation and bronchial secretions, of sweating and micturition, of gastric secretions and motility and of pupillary accommodation. Increases in heart rate, body temperature and pupillary diameter also accompany increasing doses of atropine (14). The effects associated with atropine doses of 2.0 mg or less are caused primarily by initial central stimulation followed by both peripheral and central cholinergic blockade. For the studies presently reported, we chose heart rate, blood pressure (in the second and third years), and pupillary size as representative autonomic measures.

a.4 Self-reports

Individuals who receive an atropine dose in the clinical therapeutic range (0.5 - 2.0 mg) apparently are aware of their loss of efficiency. Nuotto's (24) subjects, responding to a self-report questionnaire similar to the one developed for the present research, reported dose-related decreases in efficiency and alertness, and increased drowsiness.

a.5 Direct measurement of sleepiness

Because impaired alertness, along with weariness, reportedly increases with atropine dose, we employed in the second and third years a direct measure of sleepiness, the multiple sleep latency test, designed by Dement and his colleagues (5). Fitted with an electroencephalographic and electrooculographic recording ensemble, the subject reclines in a dark, sound-treated chamber and is invited to go to sleep. Alert, wide-awake subjects often cannot sleep at all during the 20-minute maximum recording episode, but drowsy subjects are likely to drift into stage 1 (5) sleep within a few minutes after lights out. Stage 1 is used as the index of sleep onset. The multiple sleep latency test has proved to be an extremely sensitive measure of the tendency to fall asleep, i.e., sleepiness (5). We wished to know whether a direct measure of

sleepiness was sensitive to atropine effects and whether the effects of atropine might interact with those of sleep deprivation or pre-dose exercise.

b. Effects of moderate exercise on information processing, autonomic variables, self-reports and sleep latency

b.1 Information processing

The direct effects of moderate exercise on cognitive functioning are not completely understood. Studies that used exercise interventions to investigate such effects produced conflicting findings (25). Some researchers report that exercise facilitates cognitive abilities both during and after physical exertion, whereas others report that exercise impairs mental functioning. Other investigators have found no effects of exercise on cognition. In their recent review, Tomporowski and Ellis (25) suggested that, in general, as energy output increases to an asymptotic level, so does cognitive performance, but as energy stores are depleted, cognitive performance declines. In addition, there is well-documented evidence that the effects of moderate exercise on cognitive performance are positively related to the degree of physical conditioning (25, 26, 27). However, complicating this picture, there is also evidence suggesting that to a large degree, effects of exercise on cognitive functioning are indirect, mediated by motivational variables and the subject's expectancies (25).

Studies by Carney et al. (13) showed that pre-dose exercise administered to rats could potentiate the dose effects of atropine on schedule-controlled operant behavior, and there is some evidence for similar hyperadditive effects in man (28). Such interactions suggest that assessment of the effects of pre-dose exercise in combination with atropine could increase our understanding of the role of the central cholinergic system in the support of cognitive performance.

b.2 Autonomic functions

Moderate treadmill exercise was expected to cause increases in heart rate and systolic blood pressure with no change in pupil diameter (29). It was of interest to ascertain whether the effects of pre-dose exercise on heart rate are additive or hyperadditive with those of atropine.

b.3 Self-ratings and sleep latency

In general, as pre-dose moderate exercise induces mobilization of energy resources, thereby increasing general arousal, one might anticipate some reversal of the self-reported sleepiness, weariness and loss of energy associated with the atropine dose. Moreover, increased alertness following exercise might result in increased sleep latencies in the multiple sleep latency test, thus providing objective evidence of the energizing effects of

the exercise protocol.

c. Effects of a night of sleep deprivation on information processing, autonomic variables, self-reports and sleep latency

c.1 Information processing

The most common impairment associated with loss of sleep is an inability to sustain attention to a task except with substantial mobilization of effort (30, 31). Sleep deprivation was typically thought to induce a general, nonspecific reduction of energy resources, leading to global impairment of performance. However, recent data indicate that sleep deprivation, like atropine, may selectively impair cognitive functions associated with stimulus analysis and identification. For example, Wilkinson and colleagues (32, 33), studying the effects of sleep deprivation on auditory vigilance, found a significant decline in d' but no systematic change in β after 1 night of sleeplessness. Horne et al. (34) confirmed these findings. Note, however, Naitoh's (35) recent comments on conceptual and interpretive problems associated with applications of signal detection analysis to vigilance performance. He questions whether signal detection theory and its associated statistics should ever be applied to vigilance performance of sleep deprived subjects, pointing out that frequent lapses into deep drowsiness prevent the subject from attending to every stimulus. Frequent lapses, accompanied by errors of omission, would result in increased β scores. Yet, one would not argue that the lapsing, sleep-deprived subject had adopted a more conservative response criterion.

Employing a serial stage theoretical model of reaction time along with Sternberg's (21) additive factor method, Frowein (8) and Sanders et al. (9) found that sleep loss effects interacted hyperadditively with those of two task variables, stimulus quality and time uncertainty. The effects of the several task variables were additive. When the effects on choice reaction time of certain rationally selected task variables are found to be additive, serial stage theorists infer that each task variable selectively influences a different stage of the reaction process. Thus the task variables stimulus intensity, stimulus quality, stimulus-response compatibility and time uncertainty are said to influence processing speed in a stimulus preprocessing stage, a stimulus identification stage, a response selection stage and a response preparation stage, respectively (18). If a new experimental variable such as sleep deprivation or a drug treatment shows hyperadditive interaction effects with one or more of the established task variables but has additive effects with the others, one infers that both the new experimental variable and the task variable with which it interacts influence the same stage in the reaction process. Since the effects of sleep deprivation interacted specifically with those of stimulus quality and time uncertainty and were additive with those of other established task variables, Sanders (9, 45) and Frowein (8) and their colleagues concluded that sleep deprivation slows processing

selectively in two stages of the reaction process, stimulus identification and response preparation. These hypotheses and findings supported our prediction for the second and third research years that atropine, which also influences stimulus identification functions, would show hyperadditive interaction effects with sleep deprivation.

c.2 Autonomic measures

One night of sleep deprivation can result in decreases in core body temperature, skin conductance and visual accommodation, effects that are similar to those found after atropine injection. However, a night of sleeplessness has not produced any systematic changes in heart rate or blood pressure (36, 37, 38, 39).

c.3 Self-reports and sleep latency

As would be expected, sleep-deprived subjects report decreased alertness along with increased fatigue and sleepiness (39). Sleep deprivation also causes marked reduction of sleep latencies in the multiple sleep latency test (5). Since self-ratings of sleepiness increase with atropine dose, we anticipated hyperadditive atropine by sleep loss interaction effects both on self-reports of sleepiness and on sleep latency.

4. General Experimental Methods

a. Subjects

One hundred and ten men in excellent health, ranging in age from 19 to 42, volunteered and were accepted into the research program. Volunteers were recruited by posters placed on college bulletin boards in the Oklahoma city area and from local employment placement agencies. Prospective subjects were first screened by a semistructured telephone interview conducted by a trained staff person. Callers who reported physical or psychological health problems, drug use or medication use were not admitted to the study. Although no urinalysis was actually done, each caller was asked whether he would be willing to undergo urinalysis to verify that he was drug free. If he answered, "No," he was not invited to the research center.

In a formal assessment at the research center, the volunteer read and signed a consent form and a payment contract, completed the Minnesota Multiphasic Personality Inventory and the Cornell Medical Index and received a standard physical examination conducted by an M.D. He then undertook an exercise stress test with a standard Bruce protocol (40). If he passed all of the screening examinations, he was scheduled for a series of practice days in the laboratory and for the experimental sessions. Volunteers were guaranteed a base pay and could earn bonus pay for good performance.

b. Research environment

The studies were conducted at the Oklahoma Center for Alcohol and Drug-Related Studies, which is a research unit of the Department of Psychiatry and Behavioral Sciences of the University of Oklahoma College of Medicine. The center occupies approximately 3,000 square feet of space in the Rogers Building, located at 800 N.E. 15th Street, Oklahoma City, OK 73104. The Principal Investigator is Scientific Director of the center.

c. Apparatus

The experiments were conducted in a 2.5 x 3.1 m, sound-attenuated, electrically shielded room. Timing, contingency control, stimulus presentation, response acquisition and computation of descriptive statistics (e.g., mean reaction time) were done with a Technico, System 16 microprocessor (Technico Inc., Columbia, MD). Visual stimuli were presented on an Intelligent Systems 8001 high-resolution color cathode ray tube (CRT) (Intelligent Systems Corporation, Norcross, GA) and auditory stimuli were presented with cushioned TDH-49-10z earphones (Grayson-Stadler Company, Inc., West Concord, MA).

Most of the performance tasks used in the studies were susceptible to practice effects. To control for these effects, the subjects were given practice sessions on each of 2 days before the general experimental protocols began.

The research protocols, results and conclusions for each year of the 3-year research program are presented in the following sections. To improve continuity of the narrative and to reduce redundancy, we have organized the presentation by assessment domains: thus, we first review all results and conclusions from the performance assessments; then we review the autonomic data; and so on. A general discussion follows presentation of all the results.

5. year 1: Atropine and Exercise, Performance

a. Methods

a.1 Subjects

Twelve volunteers, ranging in age from 19 to 32 (mean = 24) and weight from 140 to 210 pounds (mean = 174), completed both the atropine dose study (Experiment 1) and the atropine plus exercise study (Experiment 2). Eight others started the experimental protocol but dropped out for various reasons. Since these subjects resigned from the project at different points in the protocol, their data are not included in this report.

a.2 Research design

Two investigations were run in succession, an atropine-dose study followed by an atropine plus exercise study. Each investi-

gation employed a within-subject, repeated-measures design. The first project examined the dose-related effects of 3 i.m. doses (0.5, 1.0 and 2.0 mg) of atropine sulfate (injected into the thigh) on cognitive tasks, autonomic variables and self-reports. The atropine sulfate was supplied by Elkins-Sinn, Inc., Cherry Hill, NJ in dosette vials, each containing 1 ml (1 mg/ml) of atropine sulphate dissolved in normal saline. The dose schedule, at weekly intervals, was double-blind; and in each study, dose levels were randomized by means of a latin square. During each experimental day, there were three test cycles, each 40 minutes long, the first of which began at 1000 hours, prior to atropine injection or exercise. Atropine was injected at 1245 hours, 45 minutes prior to test cycle 2. Test cycle 3 began 60 minutes after the end of cycle 2.

The two investigations were similar in all respects except for the introduction of the moderate treadmill exercise condition in the second study. Moderate exercise was defined for each subject as 75% of his maximum heart rate in the Bruce protocol (40). Exercise began immediately after test cycle 1 and ended 15 minutes before the atropine injection.

a.3 Performance measures

There were four subtests in the battery: (1) interval estimation; (2) divided attention: interval estimation plus signal detection; (3) divided attention: compensatory tracking plus working memory; (4) oddity-matching. The two divided attention tasks were designed to load input and output functions differentially. For example, the interval estimation task differentially loads output functions, while signal detection loads input functions (41). The oddity-matching, reaction time task was chosen to investigate the effects of the experimental variables on stages in the reaction process.

(1) Interval estimation/aircraft identification

There were two types of trials, one with interval estimation only and the other with "aircraft" signals superimposed on the interval estimation task. The subject was required to estimate 15-second intervals, the beginnings of which were designated by a tone pip. If the button press signaling the subject's interval estimate occurred at 15 ± 1 seconds, a video display of a tank silhouette was presented slightly to the left or right of center on a CRT and the subject pressed one of two buttons to "fire at" and destroy the tank. The dependent variables for the interval estimation task included mean absolute error, standard deviation, skew and kurtosis of the interval estimates, percent correct interval estimates and mean reaction time to the tank presentations.

The signal detection stimuli superimposed on interval estimation in the divided attention task were two equally likely aircraft silhouettes, each 1-inch wide, differing slightly in shape.

One configuration was designated "friend" and the other, "enemy." Either 1, 2 or 3 aircraft were presented at random during each interval estimation trial in a go/no-go task. The subject was to "detect and destroy" the enemy target within a 700 msec deadline. Failure to meet the deadline resulted in a mildly aversive white flash. A false alarm (shooting at a friendly aircraft) resulted in a mildly unpleasant buzz. Bonus points, earning a financial payoff, were accrued for fast, accurate responses. Dependent variables for this task were the signal detection statistics, d', β, hits and false alarms and mean reaction time.

(2) Compensatory tracking/working memory

This task was divided into three types of trials: (1) tracking alone on a two-dimensional, compensatory tracking task; (2) mental addition alone; and (3) tracking and mental addition simultaneously. Mental addition of integers occupying either two or three places (e.g., 652 + 74) was used to load working memory. In the tracking trials, the subject manipulated a joystick positioner to counteract the apparently random movements of a cursor in two dimensions on the CRT. During each 12-second tracking trial, the computer continuously compared the observed location of the cursor with its predicted position, deriving a cumulative error score. In mental addition trials, the experimenter announced the problem, e.g., "The problem is 347 plus 32." The subject replied, "The sum of 347 plus 32 is 379." One addition problem was presented with each 12-second trial interval.

(3) Oddity-matching

On each trial, three horizontally arranged dials were presented, each containing a pointer. On each trial, the orientation of one pointer differed from that of the other two. The dials were presented at two equally likely stimulus durations (90 msec or 600 msec) and at three randomly programmed levels of intertrial intervals (30, 500 or 1000 msec). The stimulus duration variable was intended to influence input processing and the intertrial interval variable was aimed at output functions, e.g., response preparation. On each trial, the subject's task was to release a central "home" button (reaction time) and depress the button corresponding to the odd dial (motor time). Along with accuracy, the dependent variables were means and standard deviations for reaction time and motor time.

b. Results: Year 1 performance measures

b.1 Interval estimation/aircraft identification

The interval estimation task, when administered alone, proved insensitive both to atropine and to exercise. Moreover, speed and accuracy in the choice reaction time task (tank) proved to be very stable, insensitive both to atropine and to exercise.

TABLE 1

Experiment 1: Effects of Atropine and Signal Detection on Accuracy and Variability of Interval Estimation

Cycle	SDL (c)		Atropine Dose (mg) 0 Hits (a)	0 s_i (b)	0.5 Hits	0.5 s_i	1.0 Hits	1.0 s_i	2.0 Hits	2.0 s_i
1	1	$\bar{X}$	81.7	798.5	78.7	839.7	80.0	706.4	79.0	841.4
		$s_{\bar{x}}$	4.8	106.4	5.5	111.0	4.9	74.5	5.4	115.4
	2	$\bar{X}$	79.2	696.5	77.5	657.7	77.9	658.8	80.0	706.6
		$s_{\bar{x}}$	5.1	108.6	4.1	76.0	5.4	77.6	3.0	120.6
	3	$\bar{X}$	76.2	656.7	78.7	947.1	79.6	737.4	77.9	704.2
		$s_{\bar{x}}$	4.3	81.1	4.1	141.1	4.9	98.9	4.2	115.3
2	1	$\bar{X}$	82.1	647.2	83.3	740.2	78.7	874.7	72.5	966.7
		$s_{\bar{x}}$	3.2	55.1	5.0	114.4	5.1	187.0	4.8	110.0
	2	$\bar{X}$	84.2	543.5	77.5	791.7	82.1	827.8	74.6	916.2
		$s_{\bar{x}}$	4.2	42.6	7.1	143.6	4.3	184.9	4.1	126.8
	3	$\bar{X}$	73.7	576.9	73.3	760.2	74.2	849.7	69.8	819.8
		$s_{\bar{x}}$	5.9	61.3	5.3	133.6	6.1	106.5	5.8	117.8
3	1	$\bar{X}$	81.2	680.7	77.5	682.1	77.5	771.1	80.4	855.8
		$s_{\bar{x}}$	5.2	106.9	5.6	97.9	5.2	102.2	5.5	172.3
	2	$\bar{X}$	82.1	743.8	85.0	658.7	72.9	790.4	81.7	616.8
		$s_{\bar{x}}$	6.1	156.8	3.9	99.3	6.3	132.7	5.8	109.3
	3	$\bar{X}$	82.9	712.9	82.5	715.7	77.1	750.1	81.3	789.2
		$s_{\bar{x}}$	5.5	146.3	4.3	102.4	5.4	114.1	4.2	164.5

(a) Hits = average percent correct interval estimates.
(b) s_i = average standard deviation (in msec) of the subject's interval estimate distribution.
(c) SDL (signal detection load) ranges from one to three aircraft silhouettes per interval.

TABLE 2

Experiment 2: Effects of Atropine Plus Exercise and Signal Detection on Accuracy and Variability of Interval Estimation

Cycle	SDL		Atropine Dose (mg) 0 Hits	0 s_i	0.5 Hits	0.5 s_i	1.0 Hits	1.0 s_i	2.0 Hits	2.0 s_i
1	1	$\bar{X}$	78.3	884.8	82.9	922.0	85.8	714.2	80.4	821.6
		$s_{\bar{x}}$	6.7	139.8	4.6	248.9	5.3	136.4	5.7	195.8
	2	$\bar{X}$	72.9	1093.1	87.5	783.6	87.5	600.5	81.7	891.6
		$s_{\bar{x}}$	7.2	208.1	3.6	129.7	4.5	80.5	6.9	210.9
	3	$\bar{X}$	77.5	971.3	82.5	756.8	89.6	682.0	82.1	775.4
		$s_{\bar{x}}$	5.9	137.3	4.7	194.2	2.6	167.9	6.0	195.6
2	1	$\bar{X}$	88.3	733.5	87.9	677.1	79.6	859.6	77.1	972.5*
		$s_{\bar{x}}$	3.1	136.2	3.3	107.8	4.4	190.7	5.0	197.6
	2	$\bar{X}$	84.6	697.0	88.3	638.0	81.7	884.7	75.0*	974.5*
		$s_{\bar{x}}$	4.4	100.9	3.7	155.7	4.7	186.6	5.7	220.6
	3	$\bar{X}$	84.6	629.2	86.7	615.8	77.1	702.3	69.6*	1052.5*
		$s_{\bar{x}}$	3.7	70.8	2.7	91.4	4.2	105.8	5.1	227.8
3	1	$\bar{X}$	88.3	686.5	86.7	588.0	82.5	805.3	82.5	860.9
		$s_{\bar{x}}$	4.1	132.6	2.9	61.3	5.2	166.1	5.4	129.6
	2	$\bar{X}$	83.7	703.2	87.9	592.0	77.1	980.4	81.2	757.2
		$s_{\bar{x}}$	7.7	93.0	3.8	68.8	5.3	181.3	4.1	139.8
	3	$\bar{X}$	85.4	725.2	88.3	581.1	77.5	888.2	86.2	646.9
		$s_{\bar{x}}$	4.9	128.5	2.9	56.2	7.2	238.1	4.4	103.8

* $p < 0.05$.

Tables 1 (atropine alone) and 2 (atropine plus exercise) display the means ($\bar{X}$) and standard errors of the means ($s_{\bar{x}}$) for percent correct interval estimates (hits) and variability of interval estimates (s_i) at each of the three signal detection loads. The difference scores, cycle 1-cycle 2 and cycle 1-cycle 3, were each entered into 4-way, repeated-measures analyses of variance with drug dose (3 levels), exercise (2 levels), signal detection load (3 levels) and cycle (2 levels) as factors. The dose-related effect of atropine on hits was significant: $F = 5.8$, $p < 0.05$, as were the main effects of cycle, $F = 5.4$, $p < 0.05$, and the dose by cycle interaction effect, $F = 4.9$, $p < 0.05$. Analyses of simple main effects indicated that the dose effect was significant ($p < 0.05$) only at the 2.0 mg dose at cycle 2. There was also a significant dose-related increase in average s_i, $F = 5.2$, $p < 0.05$, and a significant dose by cycle interaction effect, $F = 4.9$, $p < 0.05$. The effect of atropine was again significant only at 2.0 mg and only in cycle 2. Although there were no significant main effects or interactions involving exercise, separate analyses of the two studies indicated that the atropine dose effects on interval estimation achieved statistical significance only in the atropine plus exercise study. The imposition of a signal detection load, as represented in the aircraft identification task, had no significant effects on any of the response variables associated with interval estimation.

Tables 3 and 4 display means and standard errors for the effects of atropine (Table 3) and atropine plus exercise (Table 4) on several response measures in the aircraft identification task. The atropine dose-by-cycle interaction effect on d', the measure of perceptual sensitivity, was significant, $F = 5.1$, $p < 0.05$. Analysis of simple main effects indicated that the atropine dose-related effect was significantly greater ($p < 0.05$) in cycle 3 than in cycle 2 but that the atropine effect became statistically significant only at the 2.0 mg dose. There were also significant dose effects on hits, $F = 7.5$, $p < 0.05$, and false alarms, $F = 6.1$, $p < 0.05$. Pre-dose exercise had no significant main effect on any of the response variables in aircraft signal detection, nor were there any significant interaction effects involving exercise. Finally, the signal detection index of response control, β, was not affected by any of the experimental variables.

In summary, in the interval estimation/aircraft identification divided attention task, the 2.0 mg dose of atropine produced small but statistically significant reductions in the accuracy of interval estimations, accompanied by significant increases in trial-to-trial variability of the interval estimates. However, these significant effects were found only in the second study (atropine plus exercise) and only in task cycle 2. By cycle 3, interval estimation performance had returned to baseline levels. Signal detection load (aircraft detection) had no systematic effect on any response variable associated with interval estimation. This supports the notion that the two tasks challenge different and independent processing resources; i.e., signal

TABLE 3

Effects of Atropine on Aircraft Identification

Cycle		Atropine Dose (mg) 0	0.5	1.0	2.0
			d'		
1	$\bar{X}$	2.1	2.6	3.0	2.8
	$s_{\bar{x}}$	0.3	0.4	0.5	0.2
2	$\bar{X}$	2.2	2.3	2.6	1.8
	$s_{\bar{x}}$	0.2	0.2	0.4	0.3
3	$\bar{X}$	2.6	2.5	2.5	1.1*
	$s_{\bar{x}}$	0.4	0.4	0.4	0.5
			Percent Hits		
1	$\bar{X}$	73.9	82.0	83.6	82.0
	$s_{\bar{x}}$	3.7	4.2	3.6	4.1
2	$\bar{X}$	80.7	82.9	82.0	74.9*
	$s_{\bar{x}}$	3.5	3.7	4.8	5.3
3	$\bar{X}$	85.2	82.7	84.0	76.6
	$s_{\bar{x}}$	2.9	3.8	3.9	5.0
			Percent False Alarms		
1	$\bar{X}$	13.4	10.9	8.9	11.1
	$s_{\bar{x}}$	2.1	2.1	1.5	3.1
2	$\bar{X}$	13.9	13.3	11.6	20.9*
	$s_{\bar{x}}$	2.6	2.8	2.0	3.7
3	$\bar{X}$	13.1	15.5	12.8	20.7*
	$s_{\bar{x}}$	2.5	3.1	2.1	4.0
			β		
1	$\bar{X}$	3.8	1.8	1.7	1.9
	$s_{\bar{x}}$	2.3	0.4	0.3	0.4
2	$\bar{X}$	1.8	1.6	1.2	1.8
	$s_{\bar{x}}$	0.4	0.3	0.2	0.5
3	$\bar{X}$	1.4	3.5	1.1	1.2
	$s_{\bar{x}}$	0.4	2.4	0.2	0.3

* $p < 0.05$ when compared tc cycle 1 scores.

TABLE 4

Effects of Atropine Plus Exercise on Aircraft Identification

Cycle		Atropine Dose (mg) 0	0.5	1.0	2.0
			d'		
1	$\bar{X}$	2.2	2.6	2.6	2.5
	$s_{\bar{x}}$	0.3	0.5	0.9	0.3
2	$\bar{X}$	2.9	2.8	2.0	1.7*
	$s_{\bar{x}}$	0.6	0.5	0.2	0.3
3	$\bar{X}$	3.9	2.9	1.9	1.3**
	$s_{\bar{x}}$	0.8	0.6	0.3	0.3
			Percent Hits		
1	$\bar{X}$	76.8	81.3	80.9	77.4
	$s_{\bar{x}}$	6.7	4.6	4.4	5.8
2	$\bar{X}$	83.6	85.6	78.9	72.4*
	$s_{\bar{x}}$	5.0	3.5	4.3	4.8
3	$\bar{X}$	86.0	86.9	75.5	74.2
	$s_{\bar{x}}$	4.2	3.4	5.2	4.0
			Percent False Alarms		
1	$\bar{X}$	14.0	13.2	11.0	13.2
	$s_{\bar{x}}$	4.0	3.7	2.7	3.1
2	$\bar{X}$	20.7	14.5	16.7*	17.0
	$s_{\bar{x}}$	6.6	3.8	3.2	3.5
3	$\bar{X}$	11.6	16.6	16.2	19.0*
	$s_{\bar{x}}$	3.6	4.4	3.6	3.7
			β		
1	$\bar{X}$	1.9	1.4	1.9	1.5
	$s_{\bar{x}}$	0.5	0.3	0.4	0.3
2	$\bar{X}$	1.0	1.1	1.2	1.5
	$s_{\bar{x}}$	0.2	0.2	0.2	0.2
3	$\bar{X}$	3.6	0.9	1.4	1.1
	$s_{\bar{x}}$	2.6	0.2	0.2	0.2

* $p < 0.05$ when compared to cycle 1 scores.
** $p < 0.01$.

detection probably loads input-processing functions, while interval estimation loads output functions. As predicted from work cited earlier (10, 11, 17, 18), atropine impaired aircraft identification performance by decreasing perceptual sensitivity, d', and not by altering response decision strategies, β.

b.2 Compensatory tracking/working memory

The difference scores, cycle 1-cycle 2 and cycle 1-cycle 3, were each entered into 4-way repeated-measures analysis of variance, with drug dose (3 levels), exercise (2 levels), arithmetic condition (2 levels) and cycle (2 levels) as factors. None of the experimental variables had significant main effects on tracking performance. There was, however, a significant dose by cycle interaction effect, $F = 5.5$, $p < 0.05$, for which analyses of simple main effects indicated that the atropine dose effect became significant only in cycle 2 and only at the 2.0 mg dose.

The mental addition task, intended to load working memory, proved to be insensitive to all of the experimental variables.

b.3 Oddity-matching

For each subject we computed percent correct responses and the means and standard deviations of reaction time and motor time in milliseconds. Employing the cycle 1-cycle 2 and the cycle 1-cycle 3 difference scores as dependent variables, a 5-way (dose by exercise by cycle by stimulus duration by intertrial interval) analysis of variance was performed on each response variable for percent correct and for mean reaction time and mean motor time. There were no significant effects of atropine dose, exercise or cycle. Correct responses ranged from 87 to 98% (mean = 93%) across the various conditions of the study. However, percent correct responses and reaction times were influenced by intertrial interval. Reaction times were faster and accuracy was lower at the shortest intertrial interval, $F = 19.0$, $p < 0.01$, for mean reaction time and $F = 6.9$, $p < 0.05$ for percent correct. Accuracy but not reaction time was influenced by stimulus duration, $F = 5.1$, $p < 0.05$, percent correct being lower at the shortest stimulus duration.

Atropine did have a significant dose-related effect on trial-to-trial variability (standard deviation) of reaction times. Tables 5 (atropine alone) and 6 (atropine plus exercise) contain $\bar{X}$'s and $s_{\bar{x}}$'s of the within-subject standard deviations of reaction time, as related to atropine dose, cycle, stimulus duration and intertrial interval. In both tables, trial-to-trial variability tends to increase with atropine dose, but only in cycle 2. The main effects of atropine dose were significant in each study, $F = 4.9$ for atropine alone and $F = 6.2$ for atropine plus exercise ($p < 0.05$), as were the dose by cycle interaction effects, $F = 4.9$, $p < 0.05$ for atropine alone and $F = 5.1$, $p < 0.05$ for atropine plus exercise. Analysis of simple main

TABLE 5

Effects of Atropine and Two Task Variables on Reaction Time Variability in the Oddity-matching Task

			Atropine Dose (mg)							
			0		0.5		1.0		2.0	
Cycle	ITI	SD	90(a)	600	90	600	90	600	90	600
1	30(a)	$\bar{X}$	125(b)	110	114	105	117	107	109	107
		$s_{\bar{x}}$	17	9	12	8	13	9	11	12
	500	$\bar{X}$	111	96	98	101	111	104	97	99
		$s_{\bar{x}}$	11	10	11	10	19	17	7	13
	1000	$\bar{X}$	104	95	109	99	102	108	101	93
		$s_{\bar{x}}$	9	9	13	9	14	13	9	11
2	30	$\bar{X}$	123	106	105	95	140*	121	152*	134*
		$s_{\bar{x}}$	14	7	12	48	18	17	23	11
	500	$\bar{X}$	89	84	92	95	140*	114	132*	115
		$s_{\bar{x}}$	9	8	9	8	15	16	19	21
	1000	$\bar{X}$	101	89	86	79	128*	116	122	122
		$s_{\bar{x}}$	8	5	9	8	16	24	13	22
3	30	$\bar{X}$	103	111	109	96	112	111	126	104
		$s_{\bar{x}}$	7	13	9	8	14	14	16	12
	500	$\bar{X}$	108	94	94	95	107	101	93	102
		$s_{\bar{x}}$	8	10	9	10	18	13	7	11
	1000	$\bar{X}$	100	100	94	94	104	105	125	118
		$s_{\bar{x}}$	10	11	8	10	18	17	25	16

(a) = msec.
(b) = average standard deviation scores for the within-subject reaction time distributions, in msec.
ITI = intertrial interval.
SD = stimulus deviation.
* $p < 0.05$ when compared to cycle 1 scores.

TABLE 6

Effects of Atropine Plus Exercise and Two Task Variables on Reaction time Variability in the Oddity-matching Task

			Atropine Dose (mg)							
			0		0.5		1.0		2.0	
Cycle	ITI	SD	90(a)	600	90	600	90	600	90	600
1	30(a)	$\bar{X}$	91(b)	87	86	87	100	98	119	103
		$s_{\bar{x}}$	13	13	8	14	14	11	15	15
	500	$\bar{X}$	102	89	86	76	86	81	108	112
		$s_{\bar{x}}$	20	12	14	12	10	9	18	14
	1000	$\bar{X}$	101	94	86	60	83	85	118	94
		$s_{\bar{x}}$	23	16	14	13	9	13	18	10
2	30	$\bar{X}$	130	108	110	90	114	92	179**	129*
		$s_{\bar{x}}$	35	13	30	16	14	9	13	14
	500	$\bar{X}$	92	93	111	95	123*	98*	136*	120
		$s_{\bar{x}}$	13	2	34	25	19	9	14	13
	1000	$\bar{X}$	92	103	96	97	88	88	132	101
		$s_{\bar{x}}$	4	12	30	15	9	12	17	17
3	30	$\bar{X}$	90	83	116	105	143*	96	137	116
		$s_{\bar{x}}$	18	14	29	15	19	9	17	12
	500	$\bar{X}$	79	81	93	104	104	105	105	104
		$s_{\bar{x}}$	13	13	16	20	10	13	10	11
	1000	$\bar{X}$	89	76	97	103	95	96	106	103
		$s_{\bar{x}}$	13	12	24	20	10	10	10	11

(a) = msec.
(b) = average standard deviation scores for the within-subject reaction time distribution, in msec.
* $p < 0.05$ when compared to cycle 1 scores.
** $p < 0.01$.

effects showed that the effect of atropine became statistically significant only with the 2.0 mg dose and only in task cycle 2.

In summary, analyses of variance revealed no significant main effects of atropine dose, exercise or cycle on either accuracy or average speed of performance in the oddity-matching task. The task-related variable intertrial interval did affect both accuracy and speed of performance. The other task variable, stimulus duration, also affected accuracy but neither task variable interacted with the effects of atropine. In both studies there were significant dose-related increases in trial-to-trial variability of reaction time but only in task cycle 2, at the 2.0 mg dose.

c. Conclusion: Year 1 performance measures

The hypothesis put forth by Wesnes and Warburton (17, 18) and Callaway (20) that antimuscarinic agents cause selective impairment of input perceptual processes received some support in these studies. Compared to the other tasks, the aircraft signal detection task appeared to be most sensitive to atropine dose. As predicted from the earlier findings with scopolamine (12, 18, 19, 20), atropine impaired aircraft identification performance by decreasing d' and not by altering response decision criteria or willingness to respond, β. Hits on enemy aircraft declined with atropine dose, while false alarms (shooting at friendly aircraft) increased.

Despite the sensitivity of the aircraft identification task to atropine dose, the results in Year 1 were not entirely consistent with the Warburton hypothesis. The 3-dial oddity-matching task was also designed to load input functions and it would be expected to be relatively sensitive to atropine effects. Moreover, since the task variable, stimulus duration, varied the difficulty of signal analysis, one should expect a hyperadditive interaction between the effects of stimulus durations and those of atropine. These expectations were not met. Neither average accuracy scores nor average reaction times on the oddity-matching task provided firm evidence for or against the hypothesis that atropine effects are targeted selectively on perceptual functions. Recall that a deadline procedure was used to control reaction times and the subjects were penalized for failures to meet the deadline. Under such a time constraint, accuracy rather than speed is usually the more sensitive response variable. However, the oddity-matching task was too easy. Accuracy ranged from 87 to 98% across the several conditions.

Despite the use of deadline procedures in the oddity-matching task, the 2.0 mg dose of atropine did increase trial-to-trial variability in the within-subject reaction time distributions. Significant atropine dose effects were found in both studies. The two task-related variables, stimulus duration and intertrial interval, also influenced trial-to-trial variability but neither of their effects interacted with those of atropine. Had there been a significant atropine dose by stimulus duration interaction

effect, a reasonable post-hoc inference would have related atropine-induced variability in reaction times to variability in perceptual efficiency.

Like the oddity-matching task, the bidimensional compensatory tracking task also proved to be rather insensitive to atropine effects. No main effects of atropine dose were found. There were, however, significant dose by cycle interaction effects. Tracking error increased significantly in task cycle 2 with the 2.0 mg dose. The interaction was significant ($p < 0.05$) in both the atropine alone and the atropine plus exercise studies.

The mental arithmetic task, superimposed on the compensatory tracking task, was chosen in order to study atropine effects on working memory. No dose effects were found in either study. The absence of atropine dose effects on computational accuracy in the mental arithmetic task suggests that in the dose range up to 2.0 mg, atropine does not impair working memory. The literature is not consistent on this issue. Some investigators have reported dose-related impairment of memory functions (42, 43), while other, reviewed by Headley (4), have found no atropine effects either on mathematical computation or verbal retention.

Perhaps the greatest challenge to the hypothesis that atropine selectively impairs input processes was the finding that 2.0 mg atropine was associated with increased trial-to-trial variability in the interval estimation task. Although these effects reached statistical significance only in the atropine plus exercise study and only in the divided attention protocol, the trends in the atropine alone study would probably have become significant with a modest increase in sample size. Moreover, these trends confirm those reported by McDonough (44) across a broad body of research literature. Atropine impairment of time perception has been found consistently across species. Investigations by Shingledecker et al. (41) suggest that interval estimation tasks load output-processing functions. This hypothesis receives support from our observation that nearly all subjects developed some sort of rhythmic activity, such as foot-tapping or repetitive vocalization, in the effort to keep track of time.

In the atropine plus exercise investigation, exercise alone had no systematic effects on performance. Moreover, only one performance effect favored the hypothesis that moderate exercise would enhance the potency of a subsequent dose of atropine. When atropine injection was preceded by exercise, accuracy of interval estimation declined with atropine dose. Since no significant dose-related effects on interval estimation were found in the atropine dose study, these data do suggest an atropine by exercise interaction effect. However, that interaction effect was not statistically significant.

The experience of the first year led to rather extensive modifications and changes in experimental procedures. The interval estimation task, the tracking task and mental arithmetic were

removed from the protocol, as was the entire divided attention approach. An auditory vigilance (signal detection) task was added to the protocol in order to investigate the generality of the atropine effects on perception.

6. Year 2: Atropine and Sleep Deprivation, Performance

a. Hypotheses

Recent studies (8, 9, 10, 11, 12, 17, 18, 20, 33, 34, 45) plus our first year's experience with atropine effects led to three hypotheses about the independent and combined effects of atropine and sleep deprivation on performance:

(1) A 2.0 mg dose of atropine will cause selective impairment of input perceptual functions. In both visual and auditory signal detection tasks, atropine will reduce d', the index of perceptual sensitivity, but will not influence β, the index of response control. In a visual, choice reaction time task (oddity-matching), atropine effects will interact with those of variables influencing signal quality but not with variables targeted upon such output functions as response selection and response preparation.

(2) A night of sleep deprivation will cause selective impairment of both perceptual input functions and an output function, response preparation. On both visual and auditory signal detection tasks, sleep deprivation, like atropine, will cause a decrease in d' with no change in β. On a visual choice reaction time task, sleep deprivation effects will interact hyperadditively with those of both signal quality and time uncertainty.

(3) A 2.0 mg dose of atropine and a night without sleep will have hyperadditive effects on d', hits and false alarms in visual and auditory signal detection tasks. In a choice reaction time task, a second-order interaction effect will be found involving atropine, sleep deprivation and signal quality.

b. Methods

b.1 Subjects

Thirty-two male volunteers in excellent health between 19 and 42 (mean = 28) were accepted into study. They ranged in weight from 150-190 pounds (mean = 175). They were recruited from the same sources as the first-year subjects, and after giving written informed consent, were screened for psychological or physical health problems, for substance use and abuse and for fitness (exercise stress test) exactly as in the first-year studies.

b.2 Research design

The research design was A_1BCA_2: A_1 = initial baseline, B = atropine sulfate (2.0 mg) or normal saline (placebo) adminis-

tered i.m. in the thigh, C = atropine condition plus 1 night of sleep deprivation and A_2 = final baseline. Treatments B and C were counterbalanced between subjects. Two volunteers participated each week. One was randomly selected for the atropine dose, the other, for placebo. The experiment was run double-blind.

Typically, the pair of volunteers reported to the laboratory Tuesday evening at 1900 for practice on the performance tasks. They practiced two full task cycles on Wednesday and slept in the laboratory Wednesday night. Thursday was the First baseline day, A_1. Depending on the counterbalanced design, the subjects were either deprived of sleep or not on Thursday night, remaining all night in the laboratory in either case. Friday was either session B (atropine condition alone) or session C (atropine plus sleep deprivation). The volunteers were escorted home Friday afternoon and were off until Sunday evening. They were either deprived of sleep or not Sunday night so that Monday was again either session B or C. They slept in the laboratory Monday night and Tuesday was the final baseline session, A_2. On sleepless nights, subjects were not permitted to drink caffeinated beverages but were permitted light snacks. Games, puzzles, television, radio and magazines were available. On a typical experimental day, each subject was served a light breakfast at 0700 and started task cycle 1 at 0800. Atropine or placebo was injected at 1130. Task cycles 2 and 3 began at 1210 and 1600, respectively.

b.3 Performance measures

(1) Aircraft identification

This task is a refinement of the similar task developed for the first year. At task initiation, 100 randomly located flashing red dots were presented on a black CRT background. The subject was told that these dots represented both friendly and enemy aircraft flying at the periphery of his visual detection system and that an aircraft would occasionally fly towards him. During the 15-minute task, a randomly varying number (20 to 30) of these dots were relocated to new randomly selected points on the screen. At random intervals, from 2 to 5 seconds, one of the flashing red dots began to enlarge and to assume an "approach trajectory." There were seven steps to this trajectory before the aircraft was presented head-on as friend or foe. In four out of five of these approach events, the approaches were aborted to yield "feints." In the feint events, the aircraft approached for only five of the seven steps. There were no distinguishing features and the aircraft appeared to turn and recede into the periphery. A complete approach terminated in an aircraft silhouette with a 1-inch wingspan. Friendly aircraft had wingtip tanks and enemy aircraft had tanks near the center line called "cannons."

If the silhouette was a foe, the subject was to press a

"fire" button within 700 msec. If the subject correctly detected and shot the enemy aircraft, a yellow "laser" beam intercepted the enemy craft and it exploded in yellow. A correct detection, i.e., "hit," was then recorded. If the subject failed to make the 700 msec deadline, the enemy cannons fired, causing the computer screen to flash white. An error of omission was recorded. If the subject mistakenly fired at a friendly aircraft, the aircraft exploded in blue and a false alarm was recorded. The signal detection statistics d' and β, hits and false alarms are the dependent variables of interest.

(2) Auditory vigilance

The subject heard five different 50 msec tone pips (850, 1000, 1150, 1300 and 1800 Hz), presented one at a time with an interstimulus interval of 2 seconds. The 850 Hz tone was designated the target, to which the subject was to respond with a key press. Forty-eight randomly occurring target tones were presented within each 7.5-minute trial block, with four blocks per task cycle yielding a total time on task of 30 minutes. The response variables are d', β, hits, false alarms and reaction time.

(3) Oddity-matching

This choice reaction time task was designed to investigate selective effects of atropine and sleep deprivation on stages in a serial stage theoretical model of the reaction process. The subject was presented with a series of displays, each composed of four dials arranged in a square. Each dial contained a pointer, one of which pointed in a different direction from the other three. The subject identified the odd pointer, lifted his finger from a center button (reaction time) and moved it 1 cm to press the designated one of four response buttons, also arranged in a square, as fast as he could (motor time). There were three orthogonally programmed task variables, each targeted upon a different hypothetical stage in the reaction process. These were signal quality (to influence target identification), stimulus-response compatibility (to influence response selection) and time uncertainty (to influence response preparation). Low signal quality was produced on half the trials by superimposing a random-dot mask over the CRT screen. Low stimulus-response compatibility was produced on half the trials by altering the rule for mapping the response on the stimulus. In that condition, the subject was to respond on the button located one step clockwise from the spatial location of the stimulus. Low time certainty was produced on half the trial blocks by randomly varying the interstimulus interval from 1 to 3 seconds. The oddity-matching task was experimenter paced but did not contain a specific deadline procedure. There were four blocks of trials, two with regular (1.5 second) and two with variable interstimulus intervals. The response variables of primary interest in the oddity-matching task are the means and standard deviations of the within subject reaction time and motor time distributions.

c. Results: Year 2 performance measures

c.1 Aircraft identification

(1) Atropine effects

Table 7 displays means and standard deviations for the four response variables associated with the aircraft identification task. The injection of 2.0 mg of atropine sulfate (or placebo) occurred on days B and C after task cycle 1 and about 40 minutes prior to task cycle 2. Subjects slept in the laboratory on the night of A_1 and were deprived of sleep on the night of B so that drug administration on Day C occurred after a sleepless night. Since, for some response variables, practice effects persisted through all 4 days, we used only the day B data to assess the main effects of atropine. Table 7 shows that in the atropine group on day B, d' scores decreased through test cycles 2 and 3, whereas in the placebo group, d' was relatively constant across all three test cycles. Hits declined across cycles in both the atropine and placebo conditions but the decrease was greater in the atropine group. False alarms increased in both groups but the increase was greater in the atropine group. Neither β nor reaction time showed systematic effects of atropine. Two-way, drug by cycle analyses of variance for the day B data revealed significant drug by cycle interaction effects for d' ($F = 3.5$, $p < 0.05$) and for false alarms ($F = 3.4$, $p < 0.05$), but not for hits ($F = 1.0$). Duncan's multiple range tests in the atropine group showed that the deficits in d' and false alarms became statistically significant only during cycle 3. For this reason we used only the cycle 1 and cycle 3 data in further analyses of simple main effects. One-way analyses of variance within the atropine group on day B (cycle 1-cycle 3) revealed significant effects for d' ($F = 11.4$, $p < 0.01$), hits ($F = 9.1$, $p < 0.01$) and false alarms ($F = 8.1$, $p < 0.02$). Similar analyses of simple main effects in the placebo group revealed no significant effects on cycle.

(2) Sleep deprivation effects

Recall that cycle 1 testing occurred prior to injection of drug or placebo and that on day C, cycle 1 testing followed a night of sleep deprivation. As shown in Table 7, the average d' score in cycle 1 decreased on day C in both the atropine and placebo groups. Note also the decrease in hits, the increase in false alarms and the absence of systematic trends in β scores or reaction time. To test for significant sleep-deprivation effects, we computed the difference score

$$\left(\frac{B + A_2}{2}\right) - C$$

on each response variable for each subject on the cycle 1 scores and tested the significance of this difference with t_0 for correlated means. As predicted, the effect of sleep deprivation on d' was significant, $t = 5.6$, $p < 0.001$, as were the effects on hits, $t = 3.7$, $p < 0.001$, and false alarms, $t = 3.8$, $p < 0.001$. The

TABLE 7

Effects of Atropine and Sleep State on Aircraft Identification

ATROPINE

Days(a):		A_1		B		C		A_2	
Cycle(b)		$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
1	d'	5.1	3.2	5.6	3.1	3.8	2.2	6.5	2.9
	H	92.9	8.7	95.9	4.6	86.6	18.3	97.4	6.2
	FA	6.8	11.6	4.7	9.6	8.4	9.5	3.1	4.4
	β	1.4	1.3	1.9	1.6	1.8	1.7	0.8	0.5
2	d'	5.3	2.9	5.2	2.5	2.7	1.6	6.4	2.8
	H	94.5	8.5	88.4	24.2	80.8	20.0	97.3	4.6
	FA	8.8	14.8	5.5	8.0	10.7	12.7	4.3	6.4
	β	0.9	1.2	2.1	2.1	1.7	1.0	1.2	1.6
3	d'	4.3	2.7	3.2**	1.3	1.9**	1.0	6.2	3.0
	H	94.3	6.3	91.8**	8.3	75.6*	15.8	96.9	6.3
	FA	8.4	10.1	9.1*	9.1	16.5**	14.1	5.7	11.0
	β	1.2	1.3	2.0	0.9	1.5	0.6	0.9	1.2

PLACEBO

Days(a):		A_1		B		C		A_2	
Cycle(b)		$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
1	d'	3.8	2.5	5.9	2.7	3.8"	1.8	5.6	2.4
	H	92.2	8.6	97.3	4.1	89.6"	6.3	97.6	2.4
	FA	8.1	6.5	4.3	5.4	7.0"	7.5	3.8	4.7
	β	1.0	0.7	0.7	0.6	1.3	1.9	1.4	1.6
2	d'	4.8	2.7	6.2	2.6	4.9	3.2	5.4	2.8
	H	94.2	8.0	96.7	6.0	93.5	7.2	96.9	3.6
	FA	6.0	6.1	4.4	6.2	6.4	5.9	5.3	6.4
	β	1.1	1.2	1.5	1.8	1.2	0.8	1.3	1.5
3	d'	4.1	1.9	5.7	2.6	3.7	2.4	6.3	2.5
	H	94.2	6.8	94.6	7.1	88.1	12.3	97.7	3.7
	FA	7.9	6.8	5.0	7.0	8.1	8.7	4.0	4.6
	β	1.2	1.6	2.2	2.2	2.0	1.8	1.1	1.6

(a) Days: A_1 = baseline.
B = atropine or placebo.
C = atropine or placebo + sleep deprivation.
A_2 = final baseline.

(b) Response variables: H = percent hits.
FA = percent false alarms.

* $p < 0.05$ when compared to cycle 1 scores
** $p < 0.01$
" $p < 0.01$ when compared to $(B + A_2)/2$

mean difference score for β was also statistically significant but perusal of the means in Table 7 reveals that this effect was not due to sleep deprivation. Note that in the atropine group, β showed a large drop from daily average values on A_2 and that in the placebo group, there was a large drop in β on day B. Neither group exhibited any marked change in β on day C, the sleep deprivation day. As expected with the deadline procedure employed here, sleep deprivation had no significant effect on reaction time.

(3) Effects of atropine and sleep deprivation combined

On day C all subjects had undergone a sleepless night and half the group received 2.0 mg of atropine sulfate. As illustrated in Table 7, the atropine group shows increasing impairment over test cycles on day C, while scores in the placebo group are fairly stable across test cycles. Two-way, drug by test cycle analyses of variance on the day C scores revealed significant drug by cycle interaction effects on d', $F = 9.7$, $p < 0.001$; hits, $F = 4.8$, $p < 0.02$; and false alarms, $F = 5.8$, $p < 0.01$. There were no significant effects involving β or reaction time. Analyses of simple main effects using Duncan's multiple range test showed that the atropine dose-related deficits in d', hits and false alarms reached statistical significance only in test cycle 3. To examine atropine by sleep deprivation interaction effects, we performed 2-way, drug by day (days B and C) analyses of variance on the cycle 1-cycle 3 difference scores. The main effects of drug were significant on d', $F = 6.2$, $p < 0.01$; hits, $F = 5.1$, $p < 0.02$; and false alarms, $F = 6.4$, $p < 0.01$, as were the effects of day (p values for all Fs better than 0.01). However, none of the drug by day interaction effects were statistically significant.

c.2 Auditory vigilance

A 2.0 mg dose of atropine and a sleepless night each resulted in decreased d' scores on the aircraft identification task, with no systematic change in the index of response control, β. These findings are consistent with the hypothesis that both atropine and sleep deprivation cause selective impairment of perceptual sensitivity. However, because of the tendency for atropine to impair peripheral visual acuity, it is important to learn whether atropine at 2.0 mg also impairs performance on an auditory signal detection task. Thus the auditory vigilance task was included in the test battery as a partial check on the question of whether the atropine-related impairment of aircraft identification was due primarily to peripheral impairment of visual acuity.

Tables 8a (atropine group) and 8b (placebo group) display means and standard deviations for d', hits, false alarms, and β in the auditory vigilance task. The four columns under each day represent successive 7.5-minute trial blocks. Since the task lasts about 45 minutes, it was scheduled for only two task

TABLE 8a
Effects of Atropine[a], Sleep State and Time on Task
on Response Variables in the Auditory Vigilance Task

Days:		Block A_1 1	2	3	4	Block B 1	2	3	4	Block C 1	2	3	4	Block A_2 1	2	3	4
Cycle 1(b)																	
d'	$\bar{X}$	4.8	5.2	5.2	3.6	7.5	5.9	6.2	5.4	4.5	2.9	3.3	2.5"	5.1	4.9	4.7	3.8
	s	2.9	2.9	2.8	1.8	2.8	2.9	3.3	3.6	2.0	1.2	3.1	1.0	2.0	1.9	1.7	1.0
H	$\bar{X}$	89	82	83	75	95	91	85	85	82	66	62	66"	94	84	85	83
	s	11	14	12	14	8	17	23	21	23	10	22	19	5	14	13	9
FA	$\bar{X}$	2.8	2.9	2.1	3.8	0.7	2.0	2.6	3.6	2.9	3.3	3.5	4.0"	0.9	0.6	0.7	0.6
	s	5	7	5	8	2	4	6	9	5	6	6	6	1	1	1	1
β	$\bar{X}$	2.6	3.9	4.0	4.1	3.0	3.0	3.3	3.3	3.3	4.5	3.9	4.4	3.8	4.7	4.0	5.0
	s	2.2	1.9	1.8	1.5	2.0	2.1	2.1	2.1	1.9	1.3	1.8	1.3	1.9	0.9	1.9	0.1
Cycle 2																	
d'	$\bar{X}$	4.0	4.8	4.2	4.4	3.9	4.3	4.1	4.4	2.8	2.4	2.2	2.7*	4.6	4.2	5.0	4.0
	s	1.9	2.4	2.7	2.2	1.7	3.1	2.8	2.8	0.6	0.8	0.9	1.5	2.0	2.1	2.8	1.8
H	$\bar{X}$	90	89	87	76	85	80	80	80	74	65	59	59*	92	82	85	83
	s	13	14	11	11	17	20	17	3	16	17	18	10	9	17	13	15
FA	$\bar{X}$	3.8	3.4	3.1	3.5	1.8	2.8	1.8	1.4	2.8	3.2	3.5	3.2	1.5	1.4	1.1	1.7
	s	6	7	6	7	2	4	3	2	3	4	4	5	1	2	1	2
β	$\bar{X}$	2.4	3.1	3.4	3.7	4.0	3.7	4.1	4.2	4.2	4.4	4.5	4.5	3.0	3.9	4.3	4.3
	s	2.0	2.4	2.0	2.2	1.9	1.6	1.6	1.6	1.4	1.2	1.2	1.2	1.8	1.9	1.5	1.1

(a) Atropine (2.0 mg) was injected betwen cycle 1 and cycle 2.
(b) H = percent hits; FA = percent false alarms; RT = mean reaction time; Block (column 1 - 4) = time on task (successive 7.5-minute trials).
*$p < 0.05$ when averaged across blocks and compared to cycle 1 scores.
**$p < 0.01$ when averaged across blocks and compared to $(B + A_2)/2$.

TABLE 8b
Effects of Placebo, Sleep State, and Time on Task
on Response Variables in the Auditory Vigilance Task

Days:		Block A_1				Block B				Block C				Block A_2			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Cycle 1(b)																	
d'	$\bar{X}$	4.0	3.3	3.5	3.3	5.1	3.8	4.6	3.9	2.0	1.9	2.1	2.2"	3.3	3.2	3.3	3.9
	s	2.9	2.0	2.3	2.8	4.1	3.2	3.7	3.2	1.0	1.7	1.6	1.7	2.3	2.5	2.4	3.1
H	$\bar{X}$	86	75	70	73	84	76	78	75	60	49	53	53"	79	71	74	79
	s	46	17	20	17	18	23	28	24	23	23	20	17	13	21	22	21
FA	$\bar{X}$	6.0	4.8	4.3	4.6	5.8	4.9	3.5	4.2	7.2	8.3	5.8	6.5"	7.8	7.0	5.9	6.0
	s	6.3	6.3	4.7	5.0	6.3	6.9	3.7	4.5	7.0	8.5	5.2	8.4	9.5	10.2	7.0	8.3
β	$\bar{X}$	2.3	3.8	3.7	3.3	1.6	3.4	2.6	3.2	3.2	3.2	3.4	3.8	3.6	3.7	3.5	3.0
	s	1.8	1.6	1.4	1.5	0.9	1.7	1.4	1.6	1.6	1.8	1.4	1.6	1.8	1.8	1.6	1.8
Cycle 2																	
d'	$\bar{X}$	3.2	3.6	3.4	3.2	4.4	3.0	3.9	3.7	2.0	2.0	2.0	1.9	3.3	3.0	2.9	3.0
	s	1.8	2.3	1.1	1.8	3.1	2.0	2.5	3.2	0.9	1.6	1.2	0.8	2.4	2.7	1.7	1.7
H	$\bar{X}$	84	75	68	71	84	74	78	74	62	53	49	56	79	70	72	76
	s	14	15	20	18	17	19	19	24	20	13	12	14	19	30	24	18
FA	$\bar{X}$	7.5	4.9	4.7	3.8	5.8	2.6	4.7	4.8	8.3	7.5	6.3	6.6	10.6	8.9	6.2	6.1
	s	9.5	6.1	4.9	4.3	9.5	5.4	7.7	5.0	11.1	7.0	5.7	6.5	16.0	10.7	8.3	8.6
β	$\bar{X}$	2.7	3.8	3.5	3.8	3.1	2.1	4.1	2.9	3.4	3.3	3.5	3.5	3.5	2.9	3.4	3.4
	s	1.7	1.5	1.6	1.3	1.9	1.4	1.4	1.8	1.5	1.3	1.5	1.4	1.9	1.9	1.8	1.7

H = percent hits; FA = percent false alarms; RT = mean reaction time;
Block (column 1 - 4) = time on task (successive 7.5-minute trials).
"$p < 0.01$ when averaged across blocks and compared to $(B + A_2)/2$.

cycles, one before and one about 2 hours after the atropine injection.

(1) Atropine effects

As shown in Table 8a, auditory vigilance performance tended to decline in cycle 2 after the atropine dose on day B. However, a 2 (drug) X 4 (trial blocks) analysis of variance on the cycle 1-cycle 2 difference scores found no significant effects of either atropine or time on task on any response variable. A similar analysis of drug effects on the day C difference scores did reveal significant atropine effects on d', $\underline{F} = 5.9$, $\underline{p} < 0.05$, and hits, $\underline{F} = 4.8$, $\underline{p} < 0.05$. There were no significant drug effects on β.

(2) Sleep deprivation effects

In Tables 8a and 8b, the means for cycle 1 demonstrate the same trends for the auditory vigilance task as were observed in the aircraft identification task. that is, scores on day C (sleep deprivation) show deficits. The signal detection statistics d' and hits decrease on day C, while false alarms increase. To assess the effects of sleep deprivation, cycle 1 scores on day C were compared using the average difference score

$$\left(\frac{B + A_2}{2}\right) - C$$

Two (drug) by 4 (block) analyses of variance on each response variable revealed significant sleep loss effects on d', $\underline{F} = 42.8$, $\underline{p} < 0.001$; hits, $\underline{F} = 46.7$, $\underline{p} < 0.001$; and false alarms, $\underline{F} = 21.1$, $\underline{p} < 0.001$. Sleep deprivation had no significant effects on β.

Time on task (block) had no significant effects on d', false alarms or reaction time, but hits decreased significantly over time on task, $\underline{F} = 5.0$, $\underline{p} < 0.05$, and β increased, $\underline{F} = 5.2$, $\underline{p} < 0.05$, the largest changes occurring between blocks 1 and 2. It is surprising that there were no significant sleep deprivation by blocks interaction effects. The effects of sleep deprivation and time on task are usually hyperadditive (31, 45).

(3) Effects of atropine and sleep deprivation combined

A 2.0 mg dose of atropine caused small decreases in d' and in hits in the auditory vigilance task that became statistically significant only in the sleep-deprived state. However, 2 (drug) by 2 (days B and C) analyses of variance on the cycle 1-cycle 2 difference scores showed that these interaction effects were not quite statistically significant ($\underline{p} < 0.10 > 0.05$).

c.3 Oddity-matching task

(1) Atropine effects

Table 9 contains reaction time means and standard deviations for the atropine and placebo groups on the oddity-matching task

TABLE 9

Effects of Atropine and Task Variables on
Mean Reaction Time in the Oddity-matching Task

Day B

Atropine Group (a)						Placebo Group (a)					
Cycle	SQ	SRC	TU	RT	SD	Cycle	SQ	SRC	TU	RT	SD
1	H	H	H	831	145	1	H	H	H	897	182
1	H	H	L	860	186	1	H	H	L	935	185
1	H	L	H	971	212	1	H	L	H	1020	214
1	H	L	L	1028	189	1	H	L	L	1106	240
1	L	H	H	1335	181	1	L	H	H	1299	226
1	L	H	L	1428	212	1	L	H	L	1420	262
1	L	L	H	1540	231	1	L	L	H	1540	282
1	L	L	L	1667	231	1	L	L	L	1605	262
2	H	H	H	799	155	2	H	H	H	869	171
2	H	H	L	784	141	2	H	H	L	943	177
2	H	L	H	956	181	2	H	L	H	1067	250
2	H	L	L	976	151	2	H	L	L	1123	228
2	L	H	H	1354	308	2	L	H	H	1314	196
2	L	H	L	1381	238	2	L	H	L	1399	203
2	L	L	H	1582	253	2	L	L	H	1516	253
2	L	L	L	1620	293	2	L	L	L	1589	265
3	H	H	H	797	135	3	H	H	H	856	175
3	H	H	L	862	160	3	H	H	L	888	171
3	H	L	H	1002	248	3	H	L	H	1048	301
3	H	L	L	1009	218	3	H	L	L	1122	251
3	L	H	H	1395	235	3	L	H	H	1299	194
3	L	H	L	1498	294	3	L	H	L	1440	282
3	L	L	H	1689	362	3	L	L	H	1569	263
3	L	L	L	1708*	320	3	L	L	L	1634	245

(a) SQ = signal quality;
SRC = stimulus-response compatibility;
TU = time uncertainty
RT = mean reaction time
SD = standard deviation.

*$p < 0.05$ Atropine caused a significant increase in reaction time in cycle 3, but only in the condition of low signal quality. The main effect of drug was not significant ($p > 0.05$).

for each task cycle in each task variable combination on day B. From the perspective of a serial stage model of the reaction process, the response variable of greatest interest is mean reaction time. The reaction time scores show no marked atropine main effect in the overall repeated measures multi-factorial analysis. However, hyperadditive interactions of the atropine with signal quality can be seen as consistent trends, most clearly observable in cycle 3. To make these trends in the complex design accessible for analysis, difference scores reflecting reaction time change from cycle 1 to cycle 3 were computed. The analysis of variance contained 2 levels each of drug, signal quality, stimulus-response compatibility, and time uncertainty. The drug state interacted significantly with signal quality ($F = 9.1$, $p < 0.01$). Analyses of simple main effects indicated that the effect of signal quality was significant in the atropine group ($p < 0.02$) but not in the placebo group ($F < 1.0$). Further, the atropine effect was significant only in the condition of low signal quality ($p < 0.05$). There were no other significant main effects or interaction effects involving the remaining response variables, i.e., motor time and accuracy, or the other task-related experimental variables. The significant drug by signal quality interaction effect on reaction time, and the analyses of simple main effects, suggest that atropine did cause slowing of reaction time but only in the presence of low signal quality.

The scores in Table 10, obtained from subjects in the sleep-deprived state (day C), suggest a main effect of atropine on mean reaction time. The trends in Table 10 also suggest that the drug by signal quality interaction effect on mean reaction time will again prove significant. We analyzed these effects in two steps. We first performed for day C, 2 (drug) by 2 (signal quality) by 2 (stimulus-response compatibility) by 2 (time uncertainty) analyses of variance on the cycle 1-cycle 3 difference scores for each response variable. The effect of atropine on reaction time was significant, $F = 13.5$, $p < 0.001$, as was the drug by signal quality interaction effect, $F = 10.1$, $p < 0.004$. There were no other significant main effects or interactions involving any task variable, nor were there any significant effects on motor time.

Adding the variable day (Tables 9 and 10) to the analyses of variance as a fifth experimental variable, we performed a second set of analyses of the cycle 1-cycle 3 difference scores for each response variable. For mean reaction time, the main effect of atropine was significant, $F = 10.4$, $p < 0.004$, as were the drug by day, $F = 8.5$, $p < 0.007$, and the drug by signal quality, $F = 6.7$, $p < 0.05$, interaction effects. There was no trend toward a significant three-way interaction between the effects of atropine, sleep deprivation and signal quality, $F < 1.0$. Analyses of daily effects for the two first-order interactions indicated that the drug by signal quality interaction effect was significant ($p < 0.01$) on both day B and day C. As reported earlier, on day B, the atropine dose effect was significant only

TABLE 10

Effects of Atropine, Sleep State and Task Variables on Mean Reaction Time in the Oddity-matching Task

Day C

Atropine Group (a)						Placebo Group (a)					
Cycle	SQ	SRC	TU	RT	SD	Cycle	SQ	SRC	TU	RT	SD
1	H	H	H	851	158	1	H	H	H	924	173
1	H	H	L	911	192	1	H	H	L	983	216
1	H	L	H	983	371	1	H	L	H	1122	231
1	H	L	L	1043	235	1	H	L	L	1171	200
1	L	H	H	1479	327	1	L	H	H	1517	260
1	L	H	L	1541	327	1	L	H	L	1584	210
1	L	L	H	1675	337	1	L	L	H	1753	249
1	L	L	L	1693	273	1	L	L	L	1792	186
2	H	H	H	914	201	2	H	H	H	897	155
2	H	H	L	1058	305	2	H	H	L	961	206
2	H	L	H	1129	269	2	H	L	H	1117	241
2	H	L	L	1129	238	2	H	L	L	1139	222
2	L	H	H	1675	346	2	L	H	H	1514	212
2	L	H	L	1716	352	2	L	H	L	1617	249
2	L	L	H	1858	403	2	L	L	H	1709	237
2	L	L	L	1889	316	2	L	L	L	1761	222
3	H	H	H	958	275	3	H	H	H	944	171
3	H	H	L	1009	244	3	H	H	L	933	243
3	H	L	H	1182	324	3	H	L	H	1106	290
3	H	L	L	1254	349	3	H	L	L	1092	314
3	L	H	H	1650	344	3	L	H	H	1451	341
3	L	H	L	1719	342	3	L	H	L	1442	361
3	L	L	H	1947	324	3	L	L	H	1722	345
3	L	L	L	2000	303**	3	L	L	L	1736	320

(a) SQ = signal quality;
SRC = stimulus-response compatibility;
TU = time uncertainty
RT = mean reaction time
SD = standard deviation.

**$p < 0.01$ when compared to cycle 1.

Note: On day C (sleep deprived) the main effect of atropine dose is statistically significant ($p < 0.001$). The effect is enhanced by a hyperadditive SQ by atropine interaction effect ($p < 0.004$).

in the condition of low signal quality. On day C (sleep deprived), the drug effect became significant at each level of stimulus quality, ($p < 0.01$), hence, the significant drug by day interaction effect. There were no significant effects of atropine or of any of the task-related experimental variables on motor speed.

Overall, these data indicate that a 2.0 mg dose of atropine can cause slowing of reaction time but only when performance is already degraded by certain other conditions, such as sleep deprivation or poor signal quality.

(2) Sleep deprivation effects

Table 11 contains mean task cycle 1 reaction time and motor time scores on days B, C and A_2, the final baseline day, for each condition of each task-related variable. Note that both mean reaction time and motor time tend to increase after sleep deprivation day C. For analysis of the main effects of sleep deprivation on cycle 1 scores, we computed the difference scores

$$\left(\frac{B + A_2}{2}\right) - C$$

for each subject. These differences were tested for significance, using the t-test for correlated means. Sleep deprivation caused significant increases in both reaction time, $t_0 = 5.0$, $p < 0.001$, and motor time, $t = 2.1$, $p < 0.05$. As reviewed earlier, other investigators (9, 45) predict hyperadditive effects on reaction time between sleep deprivation and two task-related experimental variables, signal quality and time uncertainty. The effects of sleep deprivation and stimulus-response compatibility should be additive. A 2 (signal quality) by 2 (stimulus-response compatibility) by 2 (time uncertainty) analysis of variance was performed on the reaction time and motor time difference scores defined above. For reaction time, the sleep deprivation by signal quality interaction was significant, $F = 23.6$, $p < 0.0001$. However, the effects of sleep deprivation were additive with both stimulus-response compatibility and time uncertainty. None of the three task variables affected motor speed.

In summary, as anticipated from Sanders et al. (9, 45), the effects of sleep deprivation on choice reaction time showed a considerable increase in the condition of low signal quality. However, the predicted sleep deprivation by time uncertainty interaction effect was not found. Nevertheless, the fact that sleep deprivation did cause significant slowing of motor speed is consistent with the hypothesis offered by Sanders (45) and Frowein et al. (46) that sleep deprivation also impairs output functions such as motor preparation.

d. Conclusion: Performance in year 2

The results from year 2 performance testing are reasonably consistent with predictions from the three hypotheses offered earlier. In the aircraft identification task, 2.0 mg of atropine

TABLE 11

Effects of Sleep State and Task Variables on Reaction Time and Motor Time in the Oddity-matching Task

Task Cycle 1 Only

Day	SQ	SRC	TU	RT	MT
B	H	H	H	864	70
B	H	H	L	898	76
B	H	L	H	995	71
B	H	L	L	1067	82
B	L	H	H	1317	72
B	L	H	L	1424	78
B	L	L	H	1540	77
B	L	L	L	1636	84
C	H	H	H	887	83
C	H	H	L	947	88
C	H	L	H	1053	79
C	H	L	L	1107	88
C	L	H	H	1498	78
C	L	H	L	1563	85
C	L	L	H	1714	96
C	L	L	L	1743**	93*
A_2	H	H	H	811	70
A_2	H	H	L	871	72
A_2	H	L	H	1003	78
A_2	H	L	L	1026	78
A_2	L	H	H	1290	74
A_2	L	H	L	1370	76
A_2	L	L	H	1497	78
A_2	L	L	L	1566	78

Day C = sleep deprived.
SQ = signal quality (H = high quality, L = low quality).
SRC = stimulus-response compatibility.
TU = time uncertainty.
RT = mean reaction time.
MT = mean motor time.
*$p < 0.05$, when averaged across the task variables and compared with $(B + A_2)/2$.
**$p < 0.01$.
Note: The effect of sleep deprivation (Day C) on RT is enhanced by a hyperadditive sleep state by SQ interaction effect, $p < 0.0001$.

caused decreases in d', the signal detection index of perceptual sensitivity, but β, the index of response control, was not affected. In the auditory vigilance task, atropine also caused decreases in d', again having no effect on β. These findings confirm and extend the results of Warburton and his colleagues (10, 11, 12, 17, 18), using scopolamine. In atropine studies, exclusive reliance on visual information-processing tasks can lead to problems of interpretation at higher doses, because the drug causes mydriasis and cycloplegia, leading to blurred vision. Our finding that auditory signal detection was as sensitive as visual signal detection to atropine is consistent with the general conclusion that the effects of moderate doses of atropine and scopolamine on perceptual sensitivity are centrally mediated.

The oddity-matching task was not as sensitive to atropine effects as the two signal detection tasks. Nevertheless, the results for this task support the first hypothesis. As predicted, atropine effects on visual choice reaction time interacted with those of stimulus quality and were additive with those of both stimulus-response compatibility and time uncertainty. Since the task variable signal quality is associated with perceptual functions, the results again imply that atropine selectively impairs input perceptual processing.

The second hypothesis, derived from the work of Sanders and his colleagues (9, 45) and Frowein et al. (8, 46), that a night of sleep deprivation would cause selective impairment of perceptual functions, was confirmed. However, the hypothesis that sleep deprivation would also impair output functions related to response preparation was only weakly supported. In both the aircraft identification task and the auditory vigilance task, sleep deprivation resulted in a reduction in d', the index of perceptual sensitivity, but had no effect on β, the index of response control. In the oddity-matching task, with mean reaction time as the principal response variable, sleep deprivation had hyperadditive interaction effects with the task variable signal quality and simple additive effects with the other two task variables, stimulus-response compatibility and time uncertainty. As summarized earlier, this pattern of results is nearly identical to that found with atropine. These data indicate that one important locus of sleep deprivation effects is in information-processing operations concerned with the acquisition of information. Whether these behavioral effects of sleep loss relate somehow to impairment of central cholinergic functioning is a question for future studies.

The third hypothesis predicted hyperadditive interactions between the effects of atropine and sleep deprivation on d' in both the aircraft identification task and the auditory vigilance task. The predicted atropine by sleep deprivation interaction effects occurred for mean reaction time in the oddity-matching task but not for aircraft identification or auditory vigilance. For example, in the aircraft identification task, the effect of atropine on d' was actually slightly less on the day following

sleep deprivation than on the day following normal sleep. This may have been due to a floor effect for these scores. Performance on task cycle 1 on day C was already impaired by a night of sleep deprivation. In the auditory vigilance task, the drug effect on d' became significant only on day C, but the atropine by sleep deprivation interaction effect was not quite statistically significant for any response variable. In the oddity-matching task, the effects of atropine on reaction time proved to be significant only when performance was degraded, either by sleep deprivation or by the task-related condition low signal quality. These overall findings suggest the presence of a three-way interaction effect on reaction time, involving atropine dose, sleep deprivation and signal quality. However, the three-way interaction effect was not significant, $F < 1.0$. Overall, these data imply that both atropine and sleep deprivation selectively influence a perceptual-analysis stage in the reaction process.

7. Year 3: Atropine, Sleep Deprivation and Exercise, Performance

a. Aims

Research in year 3 was designed to cross-validate the year 2 findings. These findings indicated that both atropine and sleep deprivation selectively influence a perceptual analysis stage of information processing. Pre-dose exercise was added to the protocol with the notion that its alerting effects might result in transient reversals of the effects of atropine and sleep deprivation.

b. Methods

b.1 Subjects

Sixty-four volunteers, screened exactly as in years 1 and 2, ranging in age from 21 to 35 (mean = 27) and in weight from 155 to 185 pounds (mean = 175), were accepted into the study. They were recruited from the same sources as the first- and second-year subjects and screened for physical and psychological problems. All gave written informed consent.

b.2 Research design

The experimental design for year 3 contained two between-group factors, atropine dose (placebo or 2.0 mg atropine sulfate, i.m.) and pre-dose exercise. Sleep state (normal sleep or a night without sleep) was a within-group factor. Paired subjects, one randomly assigned to the atropine dose and the other to placebo, were entered into the project in either the exercise or the non-exercise condition, which was counterbalanced from week to week. Neither the volunteer nor the technician knew the atropine dose assignment. Subjects began an experimental week at 0800 Tuesday and for 2 full days practiced the laboratory tasks.

The subjects were off duty from 1700 Wednesday until they returned to the laboratory Thursday evening for another practice session. Thursday night both subjects either slept (8 hours) or stayed awake through the night, undertaking the first experimental day on Friday. The subjects were tested both before and after the atropine or placebo dose from 0800-1700 Friday, after which they left the laboratory to return Sunday evening, either to sleep or to stay awake, in preparation for Monday, the second experimental day. The 2.0 mg dose of atropine sulfate in a normal saline vehicle or the placebo (normal saline) was injected into the subject's thigh at about 1200 hours on both Friday and Monday.

Moderate exercise, administered to half of the 64 subjects prior to each of the two task cycles on each experimental day, was defined as 75% of the subject's maximum heart rate. Maximum heart rate had been ascertained during the screening examination in a maximum output treadmill test using the Bruce protocol (40).

b.3 Performance assessment

The three performance tasks, aircraft identification, auditory vigilance and oddity-matching, were identical to those used in year 2 of the research. Each task was administered twice daily, once before and again about 1 1/2 hours after injection of 2.0 mg of atropine sulfate or the placebo.

c. Results: Year 3 performance measures

c.1 Aircraft identification

(1) Atropine effects

Table 12 displays means and standard deviations for the several response variables in the aircraft identification task. Note that the columns of the table represent days within exercise condition and within atropine dose and that the major rows represent task cycles within days. For ease of presentation, the column labeled day 2 always contains the scores associated with sleep deprivation. However, recall that sleep deprivation was actually counterbalanced across days. As shown in Table 12, cycle 1 testing occurred prior to the administration of atropine or placebo and cycle 2 testing occurred about 90 minutes following the injection. For those subjects in the exercise condition, exercise was scheduled prior to task cycle 1 and again prior to drug injection before cycle 2.

In Table 12, the effects of atropine dose on aircraft identification can be appraised by comparing cycle 1 to cycle 2 for the entries in the left half of the table. Note that in the atropine condition, d' and percent hits decline from cycle 1 to cycle 2, while false alarms increase. These trends are particularly marked on day 2 following a night without sleep. In the placebo condition (right half), performance scores remain relatively

TABLE 12

Effects of Atropine(a), Sleep Deprivation and Exercise on Aircraft Identification

	Atropine							
	EX				NEX			
	Day 1		Day 2		Day 1		Day 2	
	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
Cycle 1								
d'	5.5	0.5	3.7	1.8	5.9	2.2	4.4	2.1
H	96.0	9.0	93.1	8.2	98.7	1.7	95.3	5.1
FA	6.7	5.3	10.2	6.1	4.5	3.3	7.8	7.1
β	0.4	0.5	0.8	1.0	0.8	1.2	0.9	0.8
Cycle 2								
d'	4.2	2.7	2.2	1.7	4.2	2.4	2.4	0.9
H	93.2	10.0	76.6	26.0	94.7	4.6	87.2	9.5
FA	9.4	7.5	18.2	13.3	9.5	9.8	15.3	12.5
β	0.7	0.4	0.9	0.5	1.0	1.2	1.1	0.9

	Placebo							
	EX				NEX			
	Day 1		Day 2		Day 1		Day 2	
	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
Cycle 1								
d'	5.3	2.6	4.3	2.4	5.6	2.7	4.5	2.5
H	96.9	3.8	91.3	10.9	95.9	6.8	93.9	7.6
FA	6.0	5.6	6.5	6.9	7.8	10.8	8.4	12.6
β	0.6	0.6	1.7	1.7	0.7	1.2	1.4	1.5
Cycle 2								
d'	5.1	3.0	3.6	2.0	5.2	2.7	4.8	2.6
H	95.3	4.9	91.2	8.5	94.5	9.6	95.3	5.7
FA	7.2	7.9	11.2	8.4	6.5	7.1	11.6	13.4
β	1.3	1.5	1.2	1.5	1.0	1.2	1.1	1.6

(a) Atropine or placebo administered after exercise between cycle 1 and cycle 2.

Days: 1 = normal sleep.
2 - sleep deprived.

EX = pre-cycle exercise.
NEX = no exercise.
H = percent hits.
FA = percent false alarms.

stable across cycles, except for percent false alarms, which increases in cycle 2, day 2. In four-way analyses of variance (atropine dose by exercise condition by sleep state by task cycle), a significant effect of atropine on a task variable appeared as a dose by cycle interaction effect. As expected from the scores in Table 12, this two-way interaction effect was significant for d', $\underline{F} = 7.2$, $\underline{p} < 0.01$; percent hits, $\underline{F} = 12.2$, $\underline{p} < 0.001$; and percent false alarms, $\underline{F} = 5.3$, $\underline{p} < 0.03$, but not for β, $\underline{F} = 1.2$.

(2) Effects of sleep state and exercise condition

To examine performance changes due to sleep deprivation, absent any drug effects, consider the cycle 1 scores in Table 12. Compared to the day 1 scores, both d' and percent hits decreased on day 2, while percent false alarms increased. Note also small increases in β on day 2. For the scores in cycle 1, 2 by 2 (exercise condition by sleep state) analyses of variance confirmed significant main effects of sleep state on d', $\underline{F} = 14.2$, $\underline{p} < 0.002$; hits, $\underline{F} = 15.5$, $\underline{p} < 0.001$; and false alarms, $\underline{F} = 8.3$, $\underline{p} < 0.01$. There was also a small but significant increase in β on the sleep loss day, $\underline{F} = 10.3$, $\underline{p} < 0.01$, which failed to replicate in the cycle 2 data, $\underline{F} = 1.0$. In cycle 1, there were no significant main effects of exercise on any of the response variables but for percent hits, the sleep state by exercise interaction effect was nearly significant at the 0.05 level, $\underline{F} = 3.9$, $\underline{p} < 0.06$. Percent hits tended to decrease further when exercise was added to sleep deprivation.

Since atropine at a dose of 20 mg and a night without sleep each has significant main effects on several response variables of the aircraft identification task, it is important to learn whether their effects are additive or hyperadditive. As noted earlier, the changes in scores from task cycle 1 to task cycle 2 appear to be larger on day 2, particularly for percent hits. A sleep state by drug dose interaction effect would appear in tne analysis of variance as a significant three-way interaction involving sleep state, drug dose and task cycle. This effect was statistically significant for percent hits, $\underline{F} = 7.7$, $\underline{p} < 0.01$, but not for d' or percent false alarms.

In summary, as predicted from the results of year 2 of this project and from results reported by other investigators (17), both 2.0 mg dose of atropine sulfate and a night of sleep deprivation caused impairment of performance on the aircraft-identification task. The response measures, d', hits and false alarms all were sensitive to these treatments and all three variables showed trends suggesting hyperadditive two-way interactions between atropine dose and sleep state. However, this effect was statistically significant only for percent hits. There were no significant main effects of the exercise variable on performance but a two-way interaction with sleep state was just short of significance at the 0.06 level. Exercise added to the sleep-deprived condition tended to produce a further decrease in cor-

rect detections. There were no significant main effects of exercise on performance, nor were there any interaction effects involving the exercise and drug conditions.

c.2 Auditory vigilance

(1) Atropine effects

Statistical analyses indicated that among the several response variables assessed in the auditory task, d' and percent hits were sensitive to the effects of drug, sleep state and time on task. To reduce the complexity of tabular presentation, Table 13 shows means and standard deviations only for d'. As in Table 12, the columns represent days within exercise and atropine dose and the major rows represent task cycles within days. Between the major rows, trial blocks 1-6 reflect time on task. Again, systematic effects of atropine dose will be found in dose by cycle interaction effects. In five-way analyses of variance (atropine dose by sleep state by exercise condition by task cycle by task block), the dose effect proved significant for d', $F = 7.5$, $p < 0.01$, and for percent hits, $F = 18.6$, $p < 0.001$, but not for percent false alarms, $F = 1.0$, or β, $F < 1.0$.

(2) Effects of sleep state, exercise and time on task

To examine the effects of sleep state, exercise and time on task (blocks) on d', absent any drug effect, consider the entries for cycle 1. Note that in both conditions of exercise, performance declined on day 2. Note also the general decline in d' with time on task. Three-way analyses of variance (sleep state by exercise condition by task block) on the cycle 1 scores revealed significant main effects of sleep state on d', $F = 75.8$, $p < 0.001$, and on hits and false alarms ($p < 0.01$ for each measure). Performance also declined significantly with time on task, e.g., for d', $F = 9.3$, $p < 0.001$. Hits also decreased significantly with time on task ($p < 0.01$) but false alarms showed only a significant main effect of sleep state, $p < 0.01$, increasing in the sleep-deprived condition. The first-order interaction of sleep state with time on task was significant for d', $F = 4.2$, $p < 0.05$, and for hits, $p < 0.05$, but not for false alarms, $F = 1.4$. The first-order interaction of sleep state and exercise was significant for both d', $F = 9.7$, $p < 0.01$, and hits, $p < 0.01$. The impairment associated with sleep deprivation increased with both time on task and exercise. However, exercise had no significant main effects on performance.

Since d' and percent hits decreased significantly with both sleep deprivation and atropine dose, it is important to learn whether these treatment effects were additive or hyperadditive. In the five-way analyses of variance involving atropine dose, sleep state, exercise condition, task cycle and task block, the second-order interaction effect, dose by sleep state by task cycle, was significant for percent hits, $F = 4.4$, $p < 0.04$, but not for d', false alarms or β. Analyses of simple main effects

TABLE 13
Effects of Atropine Dose, Sleep State, Exercise and Time on Task on Auditory Vigilance (d')

	Atropine							
	EX				NEX			
	Day 1		Day 2		Day 1		Day 2	
	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
CYCLE 1								
Block 1	5.6	2.9	4.5	2.4	6.3	2.9	6.1	2.8
Block 2	6.1	2.8	3.7	1.4	6.4	2.4	4.7	1.8
Block 3	5.3	2.4	3.1	1.2	4.8	1.7	4.6	2.0
Block 4	5.2	2.7	3.0	1.4	5.5	2.3	4.9	1.7
Block 5	5.5	2.6	3.1	1.4	5.0	1.8	4.7	1.8
Block 6	4.6	2.4	3.9	2.3	5.2	1.5	4.5	1.5
$\bar{X}$	5.4	2.5	3.6	1.7	5.6	2.1	4.9	1.9
CYCLE 2								
Block 1	4.6	2.3	3.6	1.7	5.3	2.4	3.9	2.3
Block 2	3.8	2.3	2.6	1.1	4.6	2.1	3.3	1.6
Block 3	4.4	2.5	3.2	1.8	5.1	2.3	4.1	1.8
Block 4	4.2	2.2	2.5	1.1	3.7	2.0	3.6	1.5
Block 5	3.9	1.9	2.5	1.0	4.5	2.5	3.2	2.1
Block 6	4.1	2.0	2.6	1.5	4.2	1.6	3.2	1.4
$\bar{X}$	4.2	2.2	2.8	1.4	4.6	2.2	3.6	1.8

	Placebo							
	EX				NEX			
	Day 1		Day 2		Day 1		Day 2	
	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
CYCLE 1								
Block 1	6.7	2.9	4.3	2.1	5.5	2.9	4.8	2.6
Block 2	6.6	2.8	4.2	2.2	6.3	2.4	4.1	1.5
Block 3	5.4	2.3	3.6	1.6	5.1	2.0	4.0	1.9
Block 4	6.6	2.7	3.4	1.8	4.9	2.3	3.9	2.0
Block 5	6.2	2.4	4.2	1.8	5.3	2.4	3.7	1.4
Block 6	5.3	2.1	4.0	1.5	5.2	2.2	4.2	2.2
$\bar{X}$	6.1	2.5	4.0	1.8	5.4	2.4	4.1	1.9
CYCLE 2								
Block 1	6.1	2.9	4.4	2.3	5.5	2.3	4.1	1.7
Block 2	5.9	2.7	3.5	1.6	4.8	2.4	3.8	1.8
Block 3	5.2	2.9	3.5	1.7	4.9	1.8	3.4	1.6
Block 4	5.3	2.6	3.6	1.6	4.8	2.2	3.6	1.9
Block 5	4.5	2.3	3.1	1.4	4.8	2.0	4.2	2.2
Block 6	4.9	2.1	3.1	1.4	5.2	2.0	3.7	1.8
$\bar{X}$	5.3	2.6	3.5	1.7	5.0	2.1	3.8	1.8

Days: 1 = normal sleep; 2 = sleep deprived.
EX = pre-cycle exercise; NEX = no exercise.
Block = time on task.

TABLE 14a
Effects of Atropine Plus Exercise, Sleep State and Task Variables on Reaction Time in the Oddity-matching Task

			Atropine							
			EX				NEX			
			Day 1		Day 2		Day 1		Day 2	
SQ	SRC	TU	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
CYCLE 1										
H	H	F	911.0	245.0	902.4	284.3	945.8	261.6	953.7	259.0
H	H	V	912.6	245.6	950.3	270.8	988.8	281.2	1003.0	297.4
H	L	F	1015.1	296.3	1111.7	349.7	1079.5	308.8	1100.9	319.8
H	L	V	1017.3	286.3	1107.6	331.4	1096.6	292.0	1173.9	351.5
L	H	F	1410.3	302.2	1442.4	333.5	1379.8	282.2	1432.1	315.4
L	H	V	1445.8	277.8	1517.5	315.2	1485.6	318.8	1481.5	288.6
L	L	F	1538.6	314.5	1735.5	388.0	1633.9	355.8	1689.9	347.0
L	L	V	1599.0	322.3	1760.9	365.6	1725.6	388.0	1763.4	368.7
	$\bar{X}_t$		1231.2	286.3	1316.0	329.8	1291.9	311.1	1324.8	318.4
CYCLE 2										
H	H	F	863.5	224.1	980.8	291.8	858.8	263.9	962.2	306.2
H	H	V	967.6	279.5	1018.8	339.4	985.8	280.2	984.0	347.6
H	L	F	1038.5	303.7	1126.3	362.8	1046.0	318.7	1202.6	358.2
H	L	V	1031.3	303.2	1192.5	419.5	1115.0	381.2	1164.2	376.1
L	H	F	1453.7	342.8	1669.0	449.0	1382.0	335.1	1528.7	379.8
L	H	V	1550.8	314.0	1738.0	451.5	1481.4	296.2	1497.2	412.4
L	L	F	1659.5	384.4	1883.9	461.6	1676.9	396.0	1823.7	459.1
L	L	V	1664.9	366.0	2076.5	512.0	1728.3	382.3	1806.0	408.1
	$\bar{X}_t$		1278.7	314.7	1455.9	411.7	1284.4	331.7	1383.6	380.9

EX = exercise; NEX = no exercise.
Days: 1 = normal sleep; 2 = sleep deprived.
SQ = stimulus quality; SRC = stimulus-response compatibility; TU = time uncertainty
F = fixed intertrial interval; V = variable intertrial interval.
$\bar{X}_t$ = overall mean reaction time.

TABLE 14b
Effects of Placebo Plus Exercise, Sleep State and Task Variables on Reaction Time in the Oddity-matching Task

			Placebo							
			EX				NEX			
			Day 1		Day 2		Day 1		Day 2	
SQ	SRC	TU	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s	$\bar{X}$	s
CYCLE 1										
H	H	F	846.4	208.3	945.3	220.1	880.8	258.8	858.9	227.6
H	H	V	914.1	243.3	992.7	258.6	889.1	220.7	946.1	246.8
H	L	F	967.5	234.0	1039.5	246.2	1004.3	299.5	1040.0	298.6
H	L	V	985.0	248.1	1095.6	305.8	1013.3	274.4	1074.2	317.1
L	H	F	1298.5	288.9	1439.7	287.1	1298.1	374.0	1413.9	329.0
L	H	V	1371.0	240.8	1503.4	397.5	1399.7	301.6	1538.0	332.2
L	L	F	1424.7	299.9	1587.6	352.6	1565.3	327.7	1676.1	415.3
L	L	V	1534.5	297.0	1691.4	321.2	1612.6	372.9	1672.1	433.3
	$\bar{X}_t$		1167.7	257.5	1286.9	286.1	1207.9	291.2	1277.4	325.0
CYCLE 2										
H	H	F	869.8	241.6	926.6	234.8	848.3	325.5	879.2	274.1
H	H	V	902.4	226.6	992.3	260.6	925.6	237.0	944.5	274.9
H	L	F	1031.7	271.5	118.9	310.2	1023.8	297.8	1037.7	318.6
H	L	V	1037.5	275.6	1139.9	330.4	1005.4	291.1	1057.2	347.7
L	H	F	1333.9	255.1	1497.7	323.5	1442.6	359.9	1452.0	324.1
L	H	V	1421.3	263.0	1508.4	286.8	1522.6	359.5	1530.7	327.6
L	L	F	1546.4	311.2	1642.4	375.0	1586.5	385.0	1680.9	407.7
L	L	V	1576.9	334.6	1754.2	361.3	1616.0	323.8	1736.5	418.8
	$\bar{X}_t$		1215.0	272.4	1320.0	310.3	1246.4	311.2	1289.8	336.7

EX = exercise; NEX = no exercise.
Days: 1 = normal sleep; 2 = sleep deprived.
SQ = stimulus quality; SRC = stimulus-response compatibility; TU = time uncertainty
F = fixed intertrial interval; V = variable intertrial interval.
$\bar{X}_t$ = overall mean reaction time.

indicated that this second-order interaction effect on hits was due primarily to a relatively large decrease in hits in cycle 2 in the atropine by sleep deprivation treatment combination.

The sleep state by exercise interaction effects found in the analysis of cycle 1 scores also appeared in the overall analysis. The effect was significant for d', $F = 7.1$, $p < 0.05$, and for hits, $F = 5.2$, $p < 0.05$, but not for false alarms or β. Analyses of simple main effects indicated that performance was particularly impaired in the sleep loss by exercise treatment combination.

Research by other investigators (33, 34, 45) and our own findings in year 2 led to the prediction that sleep deprivation would have no consistent effect on the "caution" statistic, β. However, β increased significantly in cycle 1 with both sleep deprivation, $F = 13.8$, $p < 0.001$, and time on task, $F = 11.5$, $p < 0.001$. These effects were replicated in task cycle 2. As suggested by Horne et al. (34), we repeated the analyses on $\log_{10}\beta$ but the results were the same.

In summary, the results for auditory vigilance were similar to those for aircraft identification. A 2.0 mg dose of atropine and a night without sleep each impaired signal detection performance and their effects interacted to cause a considerable reduction in percent hits. The performance impairments associated with sleep deprivation increased with time on task and also with exercise, but exercise had no significant main effects on performance. As was found with the aircraft identification task, the signal detection variable, β, showed small but significant increase with both sleep loss and time on task.

c.3 Oddity-matching

(1) Atropine effects

Tables 14a and 14b display means and standard deviations for average reaction times in all treatment combinations for the oddity-matching task. As in Tables 12 and 13, the major columns show the several combinations of dose, exercise condition and sleep state and the major rows show scores for the two task cycles. The eight rows within each task cycle reflect the treatment combinations associated with the three task-related variables, signal quality, stimulus-response compatibility and time uncertainty.

A main effect of atropine dose on mean reaction time would appear as a significant dose by cycle interaction effect. In the overall analysis of variance, the dose by cycle interaction effect was not significant, $F = 2.2$, $p < 0.15$. However, the second-order interaction involving atropine dose, cycle and sleep state was statistically significant, $F = 10.7$, $p < 0.01$, as was the three-way interaction involving atropine dose, cycle and stimulus quality, $F = 5.7$, $p < 0.05$. Table 15 (a and b) displays mean reaction times for these second-order interaction effects.

As in year 2, atropine dose caused significant slowing of reaction time only when performance had been degraded, either by loss of sleep or by low signal quality.

TABLE 15a

The Second-order Interaction Effect of Atropine Dose, Sleep State and Task Cycle on Mean Reaction Time

	DOSE			
	Atropine		Placebo	
Cycle	SD	NSD	SD	NSD
1	1320	1262	1282	1188
2	1420	1282	1305	1232
Cycle 1-Cycle 2	100	20	23	43

TABLE 15b

The Second-order Interaction Effect of Atropine Dose, Display Quality and Task Cycle on Mean Reaction Time

	DOSE			
	Atropine		Placebo	
Cycle	L-DSQ	H-DSQ	L-DSQ	H-DSQ
1	1565	1017	1502	968
2	1668	1034	1553	983
Cycle 1-Cycle 2	103	17	51	15

SD = sleep deprived; NSD = normal sleep.
L-DSQ = low display quality; H-DSQ = high display quality.
Cell entries: mean reaction time in msec.

To appraise the main effect of sleep deprivation on reaction time, absent any atropine dose effect, examine the middle rows of Tables 14a and 14b (bottom of cycle 1, labeled $\bar{X}_t$). Note that overall mean reaction time shows consistent increases on day 2, the sleep loss session. Analysis of variance of mean reaction times in cycle 1, based on sleep state, exercise condition, and two levels each for the three task variables, revealed significant main effects of sleep state, $F = 21.1$, $p < 0.001$, and each of the task variables, stimulus quality, $F = 706.5$, $p < 0.001$; stimulus-response compatibility, $F = 299.9$, $p < 0.001$; and time uncertainty, $F = 46.0$, $p < 0.001$. There was not significant main effect of exercise and the exercise by sleep state interaction effect was not significant. As expected from the year 2 results, the sleep state by stimulus quality interaction effect was significant, $F = 6.4$, $p < 0.02$. Thus average reaction time for the sleep-deprived subject was particularly long when signal quality was low. There was a significant underadditive interaction between the effects of sleep state and stimulus-response compatibility such that the effect of stimulus-response compatibility was smaller in the sleep-deprived state than in the normal state. The interpretation of this effect is not obvious. There was no significant sleep state by time uncertainty interaction effect.

The analysis of mean motor times in task cycle 1 revealed a significant main effect of sleep deprivation, $F = 6.2$, $p < 0.02$, confirming the year 2 results. Exercise had no significant effect on motor time.

The overall analysis of variance with atropine dose and cycle added to the design found no significant main effect of exercise on mean reaction time, but the exercise by sleep state interaction effect was just short of statistical significance, $F = 2.9$, $p < 0.06$. The slowing of reaction time associated with sleep deprivation tended to increase following exercise.

Atropine dose had no significant main effect on mean motor time and there were no significant interaction effects on that variable.

In summary, both reaction time and motor time increased with sleep loss and as in year 2, there was a significant hyperadditive sleep state by signal quality interaction effect on reaction time. Further, as found in year 2, atropine dose caused significant slowing of reaction time only when performance had been degraded, either by sleep loss or by low signal quality. The exercise variable had no significant main effect on reaction time but did show a borderline two-way interaction with sleep state; that is, slowing due to sleep loss was most pronounced in the exercise condition.

d. Conclusion: Performance in year 3

The effects of atropine dose and sleep deprivation on the three information processing tasks replicate generally the earli-

er results from years 1 and 2, and the absence of exercise main effects on performance is consistent with the year 1 data. As had been predicted from our previous results, the 2.0 mg atropine dose impaired signal detection performance in both the aircraft identification task and the auditory vigilance task by decreasing perceptual sensitivity (d') and not by altering response decision strategies. In the oddity-matching task, atropine dose alone had no significant independent effect on reaction time but the drug did produce significant slowing when performance was degraded by low signal quality. This hyperadditive dose by signal quality interaction effect was selective in that atropine dose had simple additive effects with the other two task variables, stimulus-response compatibility and time uncertainty. Taken as a whole, these findings support the conclusion that atropine causes selective impairment of perceptual functions that are involved in signal identification.

Our results in year 2 and those in year 3 are fairly consistent with the notion that sleep deprivation also causes selective impairment of signal processing. A night without sleep resulted in decreased hits and increased false alarms (i.e., decreased d') in both the aircraft identification task and the auditory vigilance task. Unfortunately, our results for the signal detection variable (and also for $\log_{10}\beta$) were unstable from year 2 to year 3. In year 2, sleep loss had no consistent effect on β, either for the visual or the auditory detection task. In year 3, sleep loss resulted in small but significant increases in β scores in both tasks. As will be discussed later, this finding raises questions about level of motivation in our year 3 subjects.

In the oddity-matching task, the year 3 results with sleep deprivation replicated those of year 2. That is, along with a main effect on reaction time, sleep state interacted hyperadditively and selectively with the effects of signal quality. Taken together, the year 3 results support the year 2 conclusion that both atropine and sleep deprivation cause selective impairment of cognitive functions associated with signal identification. The year 3 results also replicated the atropine dose by sleep deprivation interaction effects found in year 2. These hyperadditive interaction effects indicate that the atropine by sleep loss treatment combination can place the operator at considerable risk for performance breakdown. Again, as in year 2, the second-order interaction involving atropine dose, sleep state and signal quality was not significant. The result suggest that although both atropine dose and sleep state influence functions in an encoding stage of the reaction process, they may influence independent functions within that stage. This issue will be examined further in the general discussion at the end of this report.

Moderate exercise had no significant main effects on any response variable in any of the performance tasks and there were no significant exercise condition by atropine dose interaction effects. However, hyperadditive sleep state by exercise interaction effects were found for d' and percent hits in both the

visual and auditory signal detection tasks, and the interaction bordered on significance ($p < 0.06$) for reaction time in the oddity-matching task. This potentiation of sleep loss effects by exercise was opposite from our hypotheses. We had predicted that the transient activation effects of exercise would reverse the impairments produced by sleep loss, at least over the short run.

8. Years 1, 2 and 3: Autonomic Variables, Self-reports and Sleep Latency

Heart rate, pupillary diameter and (in years 2 and 3) blood pressure were measured.

a. Heart rate

Heart rate and blood pressure were recorded and displayed with a Critikon Dynamap Vital Signs Monitor (Critikon Inc., Tampa, FL). Heart rate usually shows a biphasic response to atropine dose, with slowing at lower doses (0.4 to 0.6 mg) and progressive tachycardia at higher doses (46). The mild bradycardia at lower doses is probably due to the direct vagal stimulation known to occur prior to the onset of peripheral muscarinic cholinergic blockade (14). As expected in the atropine dose study of year 1, the 0.5 mg dose caused heart rate to slow by about 6 beats per minute (BPM). At the 2.0 mg dose, average heart rate increased by about 25-30 BPM in each experiment.

In year 1, pre-dose exercise reversed the bradycardia associated with the low dose of atropine and potentiated the accelerative effects of the 1.0 and 2.0 mg doses. The atropine dose by exercise condition interaction effect was statistically significant in year 1, $F = 10.5$, $p < 0.01$, but not in year 3, $F < 1.0$. One might expect the effects of the two treatments on heart rate to be additive rather than hyperadditive because the mechanisms of their actions are different. The tachycardia produced by atropine is caused by blockade of vagal effects on the S-A nodal pacemaker, whereas that produced by moderated exercise is due largely to sympathetic activation (47).

Sleep deprivation in years 2 and 3 had no significant effect on heart rate and there were no significant interactions involving sleep deprivation.

b. Blood pressure

Blood pressure measurement was introduced in research year 2.

In healthy subjects, blood pressure has usually not been sensitive to a 2.0 mg dose of atropine. In year 2, systolic pressure showed no systematic change with atropine dose. However, diastolic pressure did show a small but significant increase following atropine. Sleep deprivation had no effect on either measure. The atropine dose effect on diastolic pressure was replicated in year 3, $F = 5.8$, $p < 0.05$. Following the 2.0 mg

atropine injection, diastolic pressure rose from a baseline average of about 78 mm mercury to about 84 mm. Again, sleep deprivation had no effects on blood pressure.

In year 3, exercise caused a rapid and statistically significant increase in systolic blood pressure from a baseline mean of about 130 mm mercury to an average of 140 mm. Systolic levels had returned to baseline in measurements taken 1 hour following exercise. Exercise did not affect diastolic pressure. There were no significant effects of atropine dose of sleep state on systolic pressure and there were no significant interactions among the experimental variables.

In summary, atropine dose increased heart rate and diastolic pressure but had no effect on systolic pressure, while exercise increased heart rate and systolic pressure but had no effect on diastolic pressure. There were no effects of sleep state on any of the cardiovascular variables and there were no significant interaction effects among any of the experimental treatments.

c. Pupillary diameter

Pupillary data were obtained each year via 35 mm photography. A Pentax K-1000 35 mm SLR camera (Pentax, Inc., Inglewood, CO) was fitted with a 50 mm F/2 lens and Nos. 2 and 3 extension tubes. This configuration provided macro-images of 1.07 x life size at the film plane. The film was Kodak Tri-X pan 400 ISO (Eastman Kodak Co., Rochester, NY). It was developed but not printed and the negatives were projected through a 35 mm filmstrip projector onto a calibrated grid. Millimeter measurements of vertical pupil diameter were read directly from the grid.

In year 1, as expected from previous work (48), pupillary diameter increased with atropine dose but the increase became statistically significant only at the 2.0 mg dose. This finding was replicated in years 2 and 3. There were no significant main effects (or interactions) of exercise or sleep loss on pupillary size.

d. Self-ratings

The self-report questionnaire used in all 3 years consisted of 29 pairs of bipolar adjectives, each pair separated by a 6-point scale. Before and after each task cycle, the subject marked each scale interval to indicate his subjective position on several dimensions, including drowsy-alert, calm-excited, steady-dizzy, interested-bored, confused-clear thinking.

In the atropine dose condition for all 3 years, the self-report data are similar to those reported by Nuotto (24) using scopolamine. Following i.v. scopolamine, his subjects reported that they felt drowsier, mentally slower, clumsier and less efficient than they did in a nondrugged state. Following atropine dose, our subjects reported similar changes in state, and

others as well, including dreaminess, confusion and blurred vision.

The effects of exercise on self-reports were mixed and inconsistent. In year 1, subjects reported that they felt more alert, energetic and refreshed following exercise. These effects reduced some of the debilitating atropine effects to nonsignificant trends. However, in year 3, subjects in the exercise condition rated themselves less interested, less involved, less steady, less healthy, less comfortable and weaker than subjects in the nonexercise condition. It is possible that the year 3 results are more valid than those for year 1. In year 3, the exercise condition was counterbalanced between subjects. In year 1, the exercise experiment was run following the dose-response atropine study, employing the same subjects. Thus the exercise condition was confounded with time in the project.

Unfortunately, the implication that the year 3 data may be more valid than year 1 data is countered by the fact that in year 3, the self-assessments associated with sleep deprivation were clearly invalid. In year 2, sleep-deprived subjects had reported a small range of symptoms; i.e., they were less efficient, less attentive and less able to think clearly. They also reported increased dizziness and discomfort. In year 3, subjects in the sleep-deprived state gave negative self-assessments for nearly all 29 items of the questionnaire. Demand characteristics, inadvertently introduced into the experimental protocols, appear to be the most likely explanation of this behavior.

e. Sleep onset latency

During all 3 years of this research, subjects injected with atropine reported reduced alertness and increased sleepiness. In year 2, in order to examine the validity of those complaints, we introduced the multiple sleep latency test of Carskadon and Dement (5), a direct measure of sleepiness. Several times a day the subject, wearing EEG and EOG leads, was permitted to recline in a quiet, darkened, temperature-controlled bedroom and invited to go to sleep. Sleep latency (20 minutes maximum) was defined as the time between the invitation to go to sleep and onset of the first full minute of stage 1 sleep. Carskadon and Demont (5) found this test sensitive to loss of as little as 2 hours' sleep per night. In this research, the year 3 results replicated the year 2 finding, showing that 2.0 mg of atropine caused a significant reduction of sleep onset latency, i.e., increased sleepiness, thus confirming the self-report data. As expected, sleep deprivation also caused a substantial reduction in sleep onset latency. However, this effect was not so great as to mask a significant atropine dose by sleep state interaction effect. When invited to go to sleep, subjects in the placebo condition, on a normal sleep schedule, went to sleep in 10-12 minutes. Following atropine injection, sleep latency was reduced to 4-5 minutes. After a night of sleeplessness, subjects receiving placebo went to sleep in 3-5 minutes and sleep-deprived subjects

in the atropine condition were asleep in 1-2 minutes. The hyperadditive sleep state by atropine dose interaction effect was statistically significant, $p < 0.05$, in both years 2 and 3. This interaction suggests that atropine and sleep deprivation affect the same physiological functions, perhaps alerting functions mediated by the cholinergic activating system.

Moderate exercise had no significant effect on sleep latency nor were there any significant interaction effects involving exercise.

9. General Discussion

a. Performance measures

The effects of atropine and sleep deprivation on information processing were generally consistent over all 3 years of the project. The absence of exercise main effects on performance in year 3 was consistent with the year 1 data but the hyperadditive exercise by sleep state interaction effects found in year 3 were unexpected.

a.1 Atropine dose effects

As had been predicted from work on scopolamine effects by Wesnes and Warburton (17, 18) and by Callaway (20), the 2.0 mg dose of atropine impaired visual signal detection performance in all three project years by decreasing perceptual sensitivity (d') and not by altering response decision strategies (β). However, since subjects in the atropine dose condition complained of blurred vision, it became important to estimate the degree to which atropine effects on visual tasks resulted from peripheral rather than central impairment of perceptual processing. The dose-related decreases in d' found in the aircraft identification task in year 1 could have been due either to central effects of atropine or to blurring of vision caused by peripheral defects such as nydriasis or cycloplegia. It should be noted that a series of studies by Baker et al. (48) showed that our first-year findings were probably not due entirely to peripheral effects of atropine. Baker and colleagues found that basic visual function such as static visual acuity, depth perception and simple target identification were not affected by a 2.0 mg (per 70 kg body weight) dose of atropine. There is other relevant evidence. Wesnes and Warburton (18) found that methscopolamine, a peripheral cholinergic blocker, caused no impairment of a visual vigilance task that had shown scopolamine dose effects. Dunne and Hartley (22) reported that scopolamine impaired the encoding and dichotic/recall of words in dichotic listening tasks, indicating that scopolamine effects were not restricted to the visual modality. In year 2 of this research program, we added the auditory vigilance task to the test battery. Our findings in year 3 confirmed those in year 2. The 2.0 mg atropine dose impaired auditory vigilance by decreasing perceptual sensitivity (d') and not by altering response decision strategies (β). Considered

together, our findings and those of other investigators, summarized above, support the conclusion that atropine has selective effects on perceptual functions and that these effects are centrally mediated, probably by central cholinergic blockade.

In the oddity-matching task, modified in year 2, the year 3 results with atropine dose replicated those of year 2. Atropine alone had no significant main effects on reaction time but the drug did significantly slow performance when the signal quality was degraded. This hyperadditive atropine dose by stimulus quality interaction effect was selective and specific in that atropine dose showed simple additive effects with the other two task variables, stimulus-response compatibility and time uncertainty. The task variable stimulus quality is targeted on a hypothetical perceptual stage in the reaction process that we have labeled signal identification. Taken as a whole, the performance data from these 3 years of research provide firm support for the hypothesis put forth by Wesnes and Warburton (17, 18) and by Callaway (20) that antimuscarinic agents cause impairment of input processing functions, such as signal analysis, and not of output functions, such as response selection or response execution.

a.2 Sleep deprivation effects

As reviewed earlier, findings by Wilkinson and his colleagues (32, 33), Horne et al. (34), Frowein (8) and Sanders et al. (9) led to revision of commonly held views about the effects of sleep deprivation on performance. Their results support the hypothesis that sleep deprivation has selective effects on specific stage of information processing. Thus Wilkinson and colleagues (32, 33), investigating the effects of sleep loss on auditory vigilance, found declines in d' but no change in β. Frowein (8) and Sanders et al. (9), using Sternberg's (21) additive factors method with reaction time tasks, found that sleep state interacted with two task-related variables, stimulus quality and time uncertainty, on reaction time, but had simple additive effects with their other task variables, stimulus intensity and stimulus-response compatibility. Those investigators concluded that sleep deprivation caused selective impairment of two stages in the serial stage reaction process--an input stage, concerned with signal analysis, and an output stage, response preparation.

Our results in both year 2 and year 3 are fairly consistent with those summarized above. A night without sleep resulted in decreased hits and increased false alarms in both the aircraft identification task and the auditory vigilance task. These effects resulted in decreased d' scores, supporting Wilkinson's (32, 33) conclusion that sleep deprivation impairs perceptual sensitivity. Unfortunately, our results for the signal detection variable, β, were not stable from year 2 to year 3. In year 2, sleep loss had no significant effect on β in either the visual or the auditory task. In year 3, sleep loss resulted in statistically significant increases in β in both tasks. Wilkinson's

group (32, 33) had suggested that $\log_{10}\beta$ be used instead of β. We also analyzed $\log_{10}\beta$, but the results were the same. These results raised a question about the interpretation of the sleep loss-related decreases in d'. A firm interpretation of d' as the index of perceptual sensitivity rests on the assumption that β, the index of response control (i.e., decision criterion) is constant. Rising β scores could reflect a general decline in motivation to respond. Perhaps one should emphasize here that the sample size of 64 provides considerable power to detect small effects. Horne et al. (34), who found no effect of sleep deprivation on β, employed only eight subjects.

Naitoh (35) questions whether signal detection theory and its associated statistics should ever be applied to vigilance performance of sleep-deprived subjects, pointing out that signal detection analysis is based on the assumption that the subject attends to every stimulus. Frequent lapses into deep drowsiness, accompanied by errors of omission, would result in increased β scores. Yet one would not argue that the lapsing, sleep-deprived subject had adopted a more cautious criterion for positive responses. Naitoh states, "If we are really interested in the effect of sleep loss on d' and β perhaps the best experimental design will be to test psychophysically well-trained subjects not with a vigilance task, but with a signal detection task." Our auditory task is a typical vigilance task. However, our aircraft identification task might meet Naitoh's criterion for a type of signal detection task. Well-trained subjects made a response decision for each aircraft stimulus, when the stimuli were equally probably exemplars from two categories and time on task was relatively short. We agree with naitoh that the lapses of attention associated with sleepiness can create difficulties for the interpretation of d' and β. Yet it is important to learn whether findings with these signal detection variables will generalize across laboratories and across tasks.

In the oddity-matching task, the year 3 results with sleep deprivation replicated those of year 2. Along with a main effect on reaction time, sleep state effects interacted with those of stimulus quality but were additive with the effects of stimulus-response compatibility and time uncertainty. The hyperadditive interaction between effects of sleep state and signal quality confirms the findings of Sanders et al. (9). Taken together, the results from the three tasks strongly support Sanders's conclusion that sleep deprivation causes selective impairment of cognitive functions associated with signal analysis. Whether, as Sanders (45) and Frowein et al. (46) concluded, sleep loss also influences a motor adjustment stage remains a question. The finding by those investigators of a hyperadditive interaction between sleep state and time uncertainty was not replicated in the present studies. However, sleep deprivation did results in significantly increased motor times in both years. Possibly this effect is due to impairment of functions related to motor adjustment and response preparation.

a.3 Exercise effects

Moderate exercise administered prior to atropine (or placebo) injection in year 1 and year 3 had no significant main effects on any performance variable, nor were there significant interactions between exercise state and any of the task-related experimental variables. Thus exercise alone neither benefited nor impaired cognitive performance.

a.4 Interaction effects involving atropine dose, sleep state and exercise.

Since atropine and sleep deprivation both cause impairment of functions associated with signal analysis, it is important to ascertain whether these effects are additive or synergistic. If the effects of these treatments are hyperadditive, their combination could place the operator at risk for catastrophic performance breakdown. For both the aircraft identification task and the auditory vigilance task, in both year 2 and year 3, atropine dose interacted with sleep state on one of the three response variables, percent hits. Similarly, the atropine-sleep loss combination caused a considerable increase in errors of omission in the auditory vigilance task. However, for d', false alarms and β, the effects of atropine dose and sleep state were additive.

In the oddity-matching task, the interactions of atropine dose and sleep state with the task variable stimulus quality imply that each treatment slowed performance in an input stage of the reaction process. If atropine dose and sleep deprivation influence the same processing functions, their effects on reaction time should interact. The significant atropine dose by sleep state interaction effect found in year 3 replicated the year 2 finding. However, as in year 2, the three-way interaction involving stimulus quality, atropine dose and sleep state was not statistically significant. This absence of a significant second-order interaction effect suggests a more complex state of affairs than is usually considered in serial stage theoretical models of reaction time. That is, although both atropine and sleep loss influence functions in a signal analysis stage of the reaction process, each treatment may influence a different function located in that stage. For example, atropine might affect "computational processes" (9) involved in signal analysis, while sleep deprivation might affect the mobilization of deployment of energetical resources that serve selective attention. Either type of effect could cause slowing in a signal analysis stage. The possibility that both atropine and sleep loss impair the active analysis of information but that they do so via different mechanisms could be tested empirically. Thus if sleep loss affects attentional (effort) resources while atropine directly affects signal analysis operations, enhancement of effort by financial incentive might reverse the effects of sleep loss but not those of atropine. Further, if reduced energetical resources can, for the short term, be compensated by extra investment of

effort, one would predict the commonly observed sleep state by time on task interaction effect found for the auditory vigilance task in year 3. The absence of any such interaction effect involving atropine dose is also consistent with the notion that atropine and sleep loss influence different functions in a signal analysis stage.

Moderate exercise had no significant main effects on performance, either in year 1 or year 3, and there were no significant exercise condition by atropine dose interaction effects. However, in year 3, sleep state by exercise condition interaction effects were statistically significant for d' and percent hits in both the visual and auditory signal detection tasks and borderline ($p = 0.06$) for reaction time in the oddity-matching task. In each case the impairment due to sleep deprivation increased in the exercise condition. These trends were opposite from our predictions. We had anticipated that moderate exercise would produce general physiological activation, leading to improved performance by sleep-deprived subjects, at least over the short term. Incidentally, the significant exercise condition by sleep state interaction effects found for d' indicate that the additive effects on d' of the sleep loss-atropine combination were probably not the result of floor effects for d'. Again, the data suggest that atropine and sleep loss influence different functions located in a signal analysis stage.

b. Self-reports and sleep onset latency

The self-assessments associated with atropine dose were quite consistent through all 3 years of the project. Following atropine injection, subjects judged themselves to be more drowsy, lethargic and passive, less attentive, less efficient, less steady, slower and weaker. On the other hand, self-assessments associated with exercise and sleep deprivation were not consistent from year to year. For example, in year 1, pre-dose exercise tended to reverse the effects of atropine dose so that at the 2.0 mg dose, exercised subjects reported relatively less drowsiness, lethargy and inefficiency than they had reported in the no-exercise condition. In year 3, subjects in the exercise condition reported themselves to be less interested, less involved, less steady, less healthy, less comfortable and weaker than subjects in the no-exercise condition. In year 3, the items by which subjects characterized the post-exercise state showed little overlap with those that characterized the atropine state, suggesting a degree of specificity for these characterizations. Because there were several differences in research design between year 1 and year 3, it is impossible to determine which of the two sets of ratings, if either, is valid. In the year 2 data, the self-assessments associated with sleep deprivation were relatively circumscribed references to sleepiness and lethargy, along with reduced attentiveness and efficiency. In year 3, the self-assessments were clearly not valid. In the sleep-deprived state, subjects gave negative self-assessments for nearly all 29 items of the questionnaire. Demand characteristics inadvertently

introduced into the experimental protocols appear to be the most likely explanation for this behavior.

In year 2, in an effort to obtain convergent validation of the atropine dose-related complaints of reduced alertness and increased sleepiness, we introduced the multiple sleep latency task of Carskadon and Dement (5), a direct measure of sleepiness. Several times a day the subject, wearing EEG and EOG leads, reclines in a quiet, dark bedroom and is invited to go to sleep. Sleep onset latency is taken as the measure of sleepiness. The year 3 results with this test replicated the year 2 findings showing that a 2.0 mg dose of atropine caused significant reductions in sleep onset latency, thus confirming the self-report data. As expected, sleep deprivation also caused marked decreases in sleep onset latency, but this effect was not so great as to mask a significant atropine dose by sleep state interaction effect. When invited to go to sleep, sleep-deprived subjects who received 2.0 mg of atropine went to sleep immediately. This hyperadditive atropine dose by sleep state interaction effect suggest that the cholinergic arousal system may be directly involved in the induction of sleep.

We had anticipated that moderate exercise might reverse the effects of a night without sleep, arousing the subject and reducing sleepiness. However, exercise had no main effects on sleep latencies and there were no significant interaction effects involving exercise.

c. Autonomic measures

c.1 Pupillary diameter

The 2.0 mg dose of atropine caused a significant increase in pupillary diameter in all 3 years of this research. However, as reviewed earlier in this discussion, the mild mydriasis (and cycloplegia) produced are not sufficient to account for the impairments of visual information processing found in these experiments. Baker and colleagues (48) showed that basic visual functions such as simple target identification were not impaired after a 2.0 mg/70 kg atropine injection. As noted earlier, the auditory processing impairments found with the same 2.0 mg dose support the view that the information-processing deficits resulted from central rather than peripheral effects of the drug.

Neither sleep state nor exercise condition affected pupillary diameter nor were there any significant interaction effects involving those treatments.

c.2 Heart rate

The dose effects of atropine on heart rate were biphasic. At 0.5 mg, heart rate decreased, presumably because of central vagal stimulation (14). Larger atropine doses caused progressively increasing tachycardia, presumably by blocking vagal effects on

the S-A nodal pacemaker. The 2.0 mg dose of atropine caused a sharp increase in heart rate in all 3 years of the study. Exercise added to the research protocols also caused a sharp increase in heart rate, reversing the bradycardia found with the 0.5 mg atropine dose. Statistically, the effects of atropine dose and exercise condition were additive. Sleep deprivation had no effect on heart rate.

c.3 Blood pressure

Atropine in clinical doses counteracts the peripheral vasodilation and fall in blood pressure caused by choline esters (14). When given alone, its effects on blood pressure are not constant (14). However, in both year 2 and year 3 of this research, the 2.0 mg dose of atropine caused a small, statistically significant increase (about 6 mm mercury) in diastolic blood pressure with not effect on systolic pressure. In year 3, exercise caused an immediate and statistically significant increase in systolic blood pressure, averaging about 10 mm mercury, but had no effect on diastolic pressure. The effects of atropine dose and exercise on blood pressure were additive. This is expected, since the mechanisms of action of atropine and exercise on the cardiovascular system are difference. The increase in heart rate with exercise is due to direct sympathetic stimulation and the increase in systolic blood pressure is probably secondary to the increase in cardiac rate and contractility. In healthy young men, aerobic exercise also causes vasodilation in skeletal beds, tending to prevent any rise in diastolic pressure. Cholinergic blockade by atropine causes reduced vagal inhibition, resulting in large increases in heart rate. Sleep loss had no effects on cardiovascular functions and there were no significant interaction effects among any of the experimental treatments.

In summary, the results in years 2 and 3 generally confirmed predictions derived from the results for year 1 and from hypotheses proposed by other investigators (7, 8, 9, 17, 18). The 2.0 mg dose of atropine impaired cognitive functions associated with the processing of information input in both visual and auditory tasks, but did not affect functions associated with output processes. Those predictions were based on the hypothesis that the central cholinergic activating system mediates the identification and selection of task-relevant stimuli and that its blockade by muscarinic antagonists should result in impaired signal processing (10, 11, 17, 18, 20). The results for year 2 and 3 generally support the hypothesis offered by Sanders et al. (9) that sleep deprivation, like atropine, causes selective impairment of both visual and auditory input processing. The significant atropine dose by sleep state interaction effects found on several response measures imply that the two treatments influence the same stage in the reaction process. Based on the work of Sanders et al. (9) and Frowein et al. (46), we predicted a sleep state by time uncertainty interaction effect. This relationship proved to be additive in both year 1 and year 2. Thus we were unable to confirm their conclusion that sleep loss

Thus we were unable to confirm their conclusion that sleep loss also impairs one's ability to maintain a preparatory response set.

Contrary to prediction, pre-dose moderate exercise had no significant main effects on performance, in either year 1 or year 3, and there were no interaction effects involving atropine dose and exercise condition. However, exercise did potentiate the deleterious effects of sleep deprivation on all three performance tasks in year 3. We had suggested that the arousing effects of exercise might counter the de-arousing effects of sleep loss, producing transient improvements in performance, but this did no occur.

In each year of this research, self-reports showed atropine dose-related decreases in alertness, efficiency, clarity of thinking, steadiness and speed. Results in year 1 suggested that moderate pre-dose exercise could counter the self-reported atropine effects on alertness and efficiency. However, this finding was not replicated in year 3. During year 1, sleep deprivation was associated with a cluster of self-reported changes quite similar to the cluster associated with atropine dose. This finding led to introduction of the multiple sleep latency test in year 2, for direct measurement of sleepiness. Unfortunately, in year 3, sleep loss effects on self-reports were uninterpretable. Following a night of sleeplessness, the subjects endorsed the negative side of all but one of the 29 items in the self-report questionnaire.

In both year 2 and year 3, the multiple sleep latency test proved to be a valid index of the effects of atropine and of sleep loss, alone and in combination. A hyperadditive atropine dose by sleep state interaction effect on sleep latency suggested that the two variables influenced a common system. Thus cholinergic mechanisms may be directly involved in the induction and maintenance of sleep. From the perspective of military performance requirements, it is likely that the excessive daytime sleepiness caused by the atropine-sleep deprivation combination would eventually lead to catastrophic performance failures in the field, where there is a premium on sus tained vigilance ans the rapid detection and processing of stimulus information. We had predicted that the activating effects of moderate exercise might reverse the effects of sleep loss, reducing sleepiness and increasing sleep-onset latencies. However, exercise had no effects on sleep latency.

As expected from the extensive literature, the 2.0 mg dose of atropine produced tachycardia and pupillary dilation. The finding in both year 2 and year 3 that atropine also caused a significant increase in diastolic blood pressure was unexpected. As expected, moderate exercise caused large increases in heart rate, accompanied by increased systolic blood pressure with no change in diastolic pressure. As would be expected, the effects of atropine dose and exercise on the cardiovascular measures were

additive. Sleep loss had no effects on any of the autonomic variables and there were no significant interactions among the three treatments.

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